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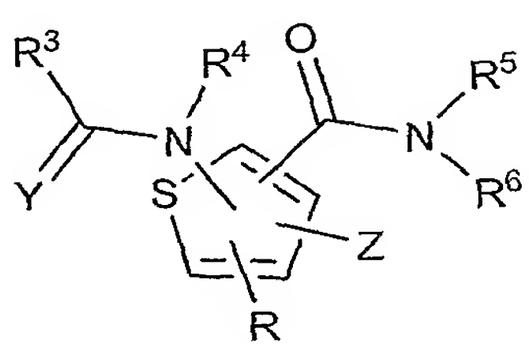
(54) Title: SUBSTITUTED THIOPHENE AMIDE COMPOUNDS FOR THE TREATMENT OF INFLAMMATION



(I)

(57) Abstract: IKK-2-inhibiting compounds of Formula I: wherein R, X, Y, Z, R^3, R^4, R^5, and are as defined herein, are disclosed.

WO 2005/105777 A1

SUBSTITUTED THIOPHENE AMIDE COMPOUNDS FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

[0001] This invention generally relates to anti-inflammatory pharmaceutical agents and specifically relates to thiophene compounds as inhibitors of IKK-2, an IκB kinase. The invention is further related to compositions comprising such compounds, and methods for treating cancer, inflammation, and inflammation-associated disorders such as arthritis.

BACKGROUND OF THE INVENTION

[0002] Rheumatoid arthritis is a common inflammatory disease affecting approximately 1% of the population. The disease is characterized by multiple painful swollen joints that severely limit the patient's daily function, and can progress to the destruction of the affected joints. A common treatment for rheumatoid arthritis is anti-inflammatory steroids. Steroids are clinically very effective, but are limited in their use because of multiple severe side-effects. Thus, a need exists for an anti- rheumatoid arthritis treatment that offers the potency of steroids without the associated toxicity. One of the mechanisms by which steroids exert their broad spectrum anti-inflammatory action is by inhibiting the activation of the transcription factor NF-κB. NF-κB plays a prominent role in immune and inflammatory responses by regulating the transcription of many early, inducible genes in a variety of cells including inflammatory enzymes such as COX-2 and iNOS. NF-κB is sequestered in an inactive form in the cytoplasm by a member of the IκB family of inhibitory proteins, and this prevents gene transcription of these responsive genes in the nucleus. Stimulation of cells leads to the phosphorylation, ubiquination and degradation of IκB thereby releasing NF-κB to the nucleus for activation of gene transcription. Chronic activation of NF-κB has been demonstrated in vascular endothelium and synovial lining cells from patients with RA. Recently the IκB kinases (IKK-1 and IKK-2), which phosphorylate IκB and thereby initiate its degradation, have been cloned and initially characterized; these kinases appear to represent the critical, common denominator in the activation of NF-κB since antisense or dominant-negative IKK constructs block NF-κB nuclear translocation and inhibit NF-κB linked reported genes. Therefore, IKK-1 and/or IKK-2 represent novel and powerful targets for drug development.

[0003] It has been reported that selective IKK-2 inhibitors could be useful for the treatment of inflammatory diseases. See, e.g., Karin et al., Nat. Revs. **3**, 17-26, 2004.

[0004] PCT Publication No. WO 01/58890 describes thiophenecarboxamides as inhibitors of IKK-2.

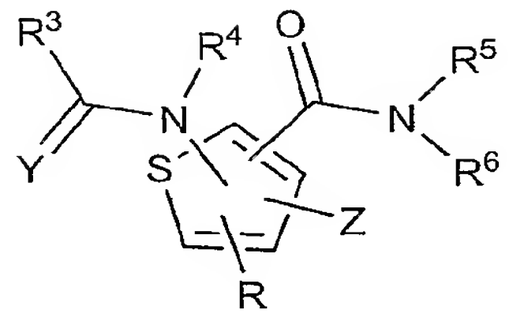
[0005] PCT Publication No. WO 02/30353 describes 2-aminothiophene-3-carboxamides as NF-κB inhibitors.

[0006] PCT Publication No. WO 03/10163 describes ureido–carboxamido thiophene compounds as inhibitors of IKK-2 kinase.

[0007] PCT Publication No. WO 03/29242 describes ureido-thiophenecarboxamide derivatives as NF-κB inhibitors.

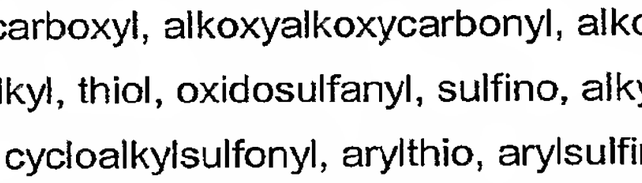
SUMMARY OF THE INVENTION

[0008] This invention provides for, in part, IKK-2-inhibiting compounds of Formula I:



[0009] I

[0010] wherein R is selected from the group consisting of:

[0011]  ;

[0012] wherein X is selected from the group consisting of a bond, alkyl, cycloalkyl, alkenyl, and heterocycloalkyl;

[0013] wherein Y is O or S;

[0014] wherein Z is selected from the group consisting of hydrido, halo, alkyl, cyano, and haloalkyl;

[0015] wherein R^1 is selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, or where R^1 and R^2 together with the atoms to which they are attached form a heterocyclic moiety, or where R^1 and R^{1a} together with the nitrogen to which they are attached form a heterocyclic moiety;

[0016] wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-alkylamino, N,N-dialkylamino, N-arylamino, N-alkyl-N-arylamino, N-hydroxyamino, N-alkyl-N-hydroxyamino, N-aryl-N-hydroxyamino, halo, cyano, keto, hydroxyl, alkyl, haloalkyl, cycloalkyl, alkoxy, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, alkoxycarbonyl, aryloxycarbonyl, carboxyl, alkoxyalkoxycarbonyl, alkoxycarbonylamino, heterocycloalkyl, heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloalkylthio, cycloalkylsulfinyl, cycloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heterocycloalkylthio, heterocycloalkylsulfinyl, heterocycloalkylsulfonyl, heteroarylthio, heteroarylsulfinyl, and heteroarylsulfonyl;

[0017] wherein R^{1a} is selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl, or where R^{1a} and R^1 together with the nitrogen to which they are attached form a heterocyclic moiety;

[0018] wherein R^2 is selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl, or R^2 and R^1 together with the atoms to which they are attached form a heterocyclic moiety;

[0019] wherein R^3 is selected from the group consisting of alkyl, haloalkyl, and $-NR^7R^8$; and

[0020] wherein R^4, R^5, R^6, R^7, and R^8 are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

[0021] or a pharmaceutically acceptable salt thereof.

[0022] The instant invention is also directed to pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically-acceptable salt thereof, as defined above, and a pharmaceutically acceptable carrier, diluent, or adjuvant.

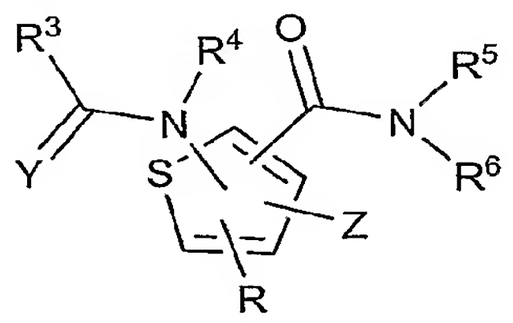
[0023] The instant invention is also directed to a method of treating or preventing inflammation or an inflammation-associated disorder, the method comprising administering a compound of Formula I or

a pharmaceutically acceptable salt thereof to a subject in need of such treatment or susceptible to such inflammation or inflammation-associated disorder.

[0024] Other objects of the invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0025] In accordance with the present invention, Applicants have discovered a class of IKK-2-inhibiting compounds of Formula I:



[0026] I

[0027] wherein R, Y, Z, R^3, R^4, R^5, and R^6 are defined as shown above.

[0028] Compounds of Formula I may be useful for treating, among other things, inflammation in a subject, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the present invention may be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis.

[0029] Compounds of the invention may be further useful in the treatment of frailty, asthma, chronic obstructive pulmonary disease (COPD), bronchitis, menstrual cramps (e.g., dysmenorrhea), premature labor, tendinitis, bursitis, dermatological conditions such as psoriasis, eczema, burns, sunburn, dermatitis, pancreatitis, hepatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compounds of the invention would be useful for the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix and skin, as well as treatment of cancer stem cells. Compounds of the invention would be useful in treating inflammation and tissue damage in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

[0030] The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, and central nervous system damage resulting from stroke, ischemia and trauma. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, and atherosclerosis. The compounds would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular

pain, and pain resulting from cancer. The compounds would be useful for the prevention of dementias, such as Alzheimer's disease.

[0031] Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

[0032] The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatory therapies, such as together with steroids, NSAIDs, COX-2 selective inhibitors, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

[0033] Other conditions in which the compounds of the present invention may provide an advantage include cardiovascular ischemia, diabetes (type I or type II), congestive heart failure, myocarditis, atherosclerosis, migraine, glaucoma, aortic aneurysm, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, asthma, bronchiectasis, hyperalgesia (allodynia), and cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia (for example, secondary to cardiac arrest).

[0034] The compounds of the present invention may also be useful in the treatment of pain including somatogenic (either nociceptive or neuropathic), both acute and chronic. A compound of the present invention could be used in any situation including neuropathic pain that a common NSAID or opioid analgesic would traditionally be administered.

[0035] Conjunctive treatment of a compound of the present invention with an antineoplastic agent may produce a beneficial effect or alternatively reduce the toxic side effects associated with chemotherapy by reducing the therapeutic dose of the side effect-causing agent needed for therapeutic efficacy or by directly reducing symptoms of toxic side effects caused by the side effect-causing agent. A compound of the present invention may further be useful as an adjunct to radiation therapy to reduce side effects or enhance efficacy. In the present invention, another agent which can be combined therapeutically with a compound of the present invention includes any therapeutic agent which is capable of inhibiting the enzyme cyclooxygenase-2 ("COX-2"). Preferably such COX-2 inhibiting agents inhibit COX-2 selectively relative to the enzyme cyclooxygenase-1 ("COX-1"). Such a COX-2 inhibitor is known as a "COX-2 selective inhibitor". More preferably, a compound of the present invention can be therapeutically combined with a COX-2 selective inhibitor wherein the COX-2 selective inhibitor selectively inhibits COX-2 at a ratio of at least 10:1 relative to inhibition of COX-1, more preferably at least 30:1, and still more preferably at least 50:1 in an *in vitro* test. COX-2 selective inhibitors useful in therapeutic combination with the compounds of the present invention include celecoxib, valdecoxib, deracoxib, etoricoxib, rofecoxib, ABT-963 (2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone; described in PCT Publication No. WO 00/24719), or meloxicam. A compound of the present invention can also be advantageously used in therapeutic combination with a prodrug of a COX-2 selective inhibitor, for example parecoxib.

[0036] Another chemotherapeutic agent which may be useful in combination with a compound of the present invention can be selected, for example, from the following non-comprehensive and non-limiting list: Alpha-difluoromethylornithine (DFMO), 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrill Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine,

fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT, uricytin, Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin, trimelamol, Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 zorubicin, alpha-carotene, alpha-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristo-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemex CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, elliprabin, elliptinium acetate, Tsumura

EPMTC, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone, mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides, Yamanouchi YM-534, uroguanylin, combretastatin, dolastatin, idarubicin, epirubicin, estramustine, cyclophosphamide, 9-amino-2-(S)-camptothecin, topotecan, irinotecan (Camptosar), exemestane, decapeptyl (tryptorelin), or an omega-3 fatty acid.

[0037] Examples of radioprotective agents which may be used in a combination therapy with the compounds of this invention include AD-5, adchnon, amifostine analogues, detox, dimesna, I-102, MM-159, N-acylated-dehydroalanines, TGF-Genentech, tiprotimod, amifostine, WR-151327, FUT-187, ketoprofen transdermal, nabumetone, superoxide dismutase (Chiron) and superoxide dismutase Enzon.

[0038] The compounds of the present invention may also be useful in treatment or prevention of angiogenesis-related disorders or conditions, for example, tumor growth, metastasis, macular degeneration, and atherosclerosis.

[0039] In a further embodiment, the present invention also provides therapeutic combinations for the treatment or prevention of ophthalmic disorders or conditions such as glaucoma. For example the present inventive compounds advantageously may be used in therapeutic combination with a drug which reduces the intraocular pressure of patients afflicted with glaucoma. Such intraocular pressure-reducing drugs include without limitation latanoprost, travoprost, bimatoprost, or unoprostol. The therapeutic combination of a compound of the present invention plus an intraocular pressure-reducing drug may be useful because each is believed to achieve its effects by affecting a different mechanism.

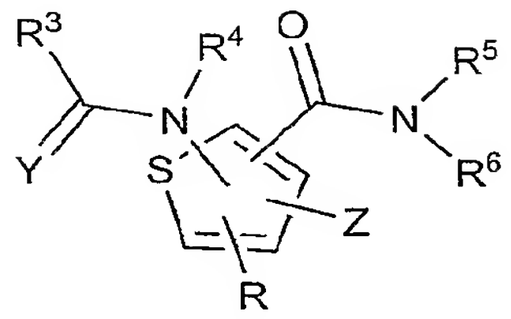
[0040] In another combination of the present invention, the present inventive compounds can be used in therapeutic combination with an antihyperlipidemic or cholesterol-lowering drug such as a benzothiepine or a benzothiazepine antihyperlipidemic drug. Examples of benzothiepine antihyperlipidemic drugs useful in the present inventive therapeutic combination can be found in U.S. Patent No. 5,994,391, herein incorporated by reference. Some benzothiazepine antihyperlipidemic drugs are described in PCT Publication No. WO 93/16055. Alternatively, the antihyperlipidemic or cholesterol-lowering drug useful in

combination with a compound of the present invention can be an HMG Co-A reductase inhibitor. Examples of HMG Co-A reductase inhibitors useful in the present therapeutic combination include, individually, benfluorex, fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, ZD-9720 (described in PCT Publication No. WO 97/06802), ZD-4522 (CAS No. 147098-20-2 for the calcium salt; CAS No. 147098-18-8 for the sodium salt; described in European Patent No. EP 521471), BMS 180431 (CAS No. 129829-03-4), or NK-104 (CAS No. 141750-63-2). The therapeutic combination of a compound of the present invention plus an antihyperlipidemic or cholesterol-lowering drug may be useful, for example, in reducing the risk of formation of atherosclerotic lesions in blood vessels. For example, atherosclerotic lesions often initiate at inflamed sites in blood vessels. It is established that antihyperlipidemic or cholesterol-lowering drug reduce risk of formation of atherosclerotic lesions by lowering lipid levels in blood. Without limiting the invention to a single mechanism of action, it is believed that one way the compounds of the present combination may work in concert to provide improved control of atherosclerotic lesions by, for example, reducing inflammation of the blood vessels in concert with lowering blood lipid levels.

[0041] In another embodiment of the invention, the present compounds can be used in combination with other compounds or therapies for the treatment of central nervous conditions or disorders such as migraine. For example, the present compounds can be used in therapeutic combination with caffeine, a 5-HT-1B/1D agonist (for example, a triptan such as sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, or frovatriptan), a dopamine D4 antagonist (e.g., sonepiprazole), aspirin, acetaminophen, ibuprofen, indomethacin, naproxen sodium, isometheptene, dichloralphenazone, butalbital, an ergot alkaloid (e.g., ergotamine, dihydroergotamine, bromocriptine, ergonovine, or methyl ergonovine), a tricyclic antidepressant (e.g., amitriptyline or nortriptyline), a serotonergic antagonist (e.g., methysergide or cyproheptadine), a beta-andrenergic antagonist (e.g., propranolol, timolol, atenolol, nadolol, or metprolol), or a monoamine oxidase inhibitor (e.g., phenylzine or isocarboxazid).

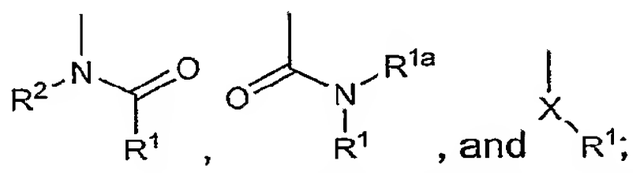
[0042] The present invention includes compounds that selectively inhibit IKK-2 over other kinases. Such other kinases include, but are not limited to, Abl(h), Abl(T315I), Abl(T315I), AMPK, Aurora-A, BTK, CaMKII, CaMKIV, CDK1/cyclinB, CDK2, CDK2/cyclin A, CDK2/cyclinE, CHK1, CHK2, CK1, CK1(y), CK1δ, CK2, c-RAF(h), CSK, cSRC(h), DYRK1a, ERK2, Fyn, GSK3ß, IGF-1R, IKK1, IKKi, IKK2(h), JNK/SAPK1c, JNK1, JNK1α1(h), JNK2, JNK2α2(h), JNK3, Lck, MAPK1(h), MAPK2(h), MAPK2/ERK2, MAPKAP-K1a, MAPKAP-K2, MEK1, MK-2, MK-3, MKK1, MKK4, MKK6, MKK7, MKK7ß(h), MNK, MRSK2/APKAPk1b, MSK, MSK1, NEK2a, NEK6, p38 alpha, p38 beta, p38 delta, p38 gamma, p70 S6K, PAK2, PDGFRß, PDK1, PHK, PKA, PKBΔph, PKCζ, PKCα, PKCγ, PKCδ, PKCϵ, PRAK, ROCK-II, Rsk1, Rsk2, RSKB, SAPK2a/p38, SAPK2b, SAPK2b/p38ß2, SAPK3, SAPK3/p38g, SAPK4, SAPK4/p38d, SGK, TBK-1, and ZAP-70. The compounds may have an IKK-2 IC_{50} of less than about 10 μM, preferably less than about 1 μM, and have a selectivity ratio of IKK-2 inhibition over IKK-1 inhibition of at least 50, or at least 100. The compounds may have an IKK-1 IC_{50} of greater than 10 μM, or greater than 100 μM.

[0043] In one preferred embodiment, the compound of Formula I is a compound of Formula IA:



[0044] IA

[0045] wherein R is selected from the group consisting of:



[0046]

[0047] wherein X is selected from the group consisting of a bond, alkyl, cycloalkyl, alkenyl, and heterocycloalkyl;

[0048] wherein Z is selected from the group consisting of hydrido, halo, alkyl, cyano, and haloalkyl;

[0049] wherein R^1 is selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, or where R^1 and R^2 together with the atoms to which they are attached form a heterocyclic moiety, or where R^1 and R^{1a} together with the nitrogen to which they are attached form a heterocyclic moiety;

[0050] wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-alkylamino, N,N-dialkylamino, N-arylamino, N-alkyl-N-arylamino, N-hydroxyamino, N-alkyl-N-hydroxyamino, N-aryl-N-hydroxyamino, halo, cyano, keto, hydroxyl, alkyl, haloalkyl, cycloalkyl, alkoxy, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, alkoxycarbonyl, aryloxycarbonyl, carboxyl, alkoxyalkoxycarbonyl, alkoxycarbonylamino, heterocycloalkyl, heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloalkylthio, cycloalkylsulfinyl, cycloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heterocycloalkylthio, heterocycloalkylsulfinyl, heterocycloalkylsulfonyl, heteroarylthio, heteroarylsulfinyl, and heteroarylsulfonyl;

[0051] wherein R^{1a} is selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl, or where R^{1a} and R^1 together with the nitrogen to which they are attached form a heterocyclic moiety;

[0052] wherein R^2 is selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl, or R^2 and R^1 together with the atoms to which they are attached form a heterocyclic moiety;

[0053] wherein R^3 is selected from the group consisting of alkyl, haloalkyl, and $-NR^7R^8$; and

[0054] wherein R^4, R^5, R^6, R^7, and R^8 are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

[0055] or a pharmaceutically acceptable salt thereof.

[0056] In one preferred embodiment, the compound of Formula IA is a compound wherein X is selected from the group consisting of a bond, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{2-6} alkenyl, and 3- to 12-membered heterocycloalkyl;

[0057] wherein Z is selected from the group consisting of hydrido, halo, C_{1-6} alkyl, cyano, and C_{1-6} haloalkyl;

[0058] wherein R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{2-6} alkenyl, C_{3-12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{3-12} aryl, C_{4-18} aralkyl, 3- to 12-membered heteroaryl, and 4- to 18-membered heteroaralkyl, or where R^1 and R^2 together with the atoms to which they are attached form a 3- to 12-membered heterocyclic moiety, or where R^1 and R^{1a} together with the nitrogen to which they are attached form a 3- to 12-membered heterocyclic moiety;

[0059] wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{3-12} aryl)amino, N-(C_{1-6} alkyl)-N-(C_{3-12} aryl)amino, N-hydroxyamino, N-(C_{1-6} alkyl)-N-hydroxyamino, N-(C_{3-12} aryl)-N-hydroxyamino, halo, cyano, keto, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkenyloxy, C_{3-12} aryl, C_{3-12} aryloxy, C_{4-20} aralkyl, C_{4-20} aralkylcarbonyl, C_{4-20} aralkylcarbonylamino, 3- to 14-membered heteroarylcarbonyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 3- to 12-membered heteroaryl, C_{2-7} alkoxycarbonyl, C_{3-12} aryloxycarbonyl, carboxyl, C_{2-15} alkoxyalkoxycarbonyl, C_{2-7} alkoxycarbonylamino, 3- to 12-membered heterocycloalkyl, 4- to 18-membered heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{3-12} cycloalkylthio, C_{3-12} cycloalkylsulfinyl, C_{3-12} cycloalkylsulfonyl, C_{3-12} arylthio, C_{3-12} arylsulfinyl, C_{3-12} arylsulfonyl, 3- to 12-membered heterocycloalkylthio, 3- to 12-membered heterocycloalkylsulfinyl, 3- to 12-membered heterocycloalkylsulfonyl, 3- to 12-membered heteroarylthio, 3- to 12-membered heteroarylsulfinyl, 3- to 12-membered and heteroarylsulfonyl;

[0060] wherein R^{1a} is selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl, or where R^{1a} and R^1 together with the nitrogen to which they are attached form a 3- to 12-membered heterocyclic moiety;

[0061] wherein R^2 is selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl, or R^2 and R^1 together with the atoms to which they are attached form a 3- to 12-membered heterocyclic moiety;

[0062] wherein R^3 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, and $-NR^7R^8$; and

[0063] wherein R^4, R^5, R^6, R^7, and R^8 are independently selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl.

[0064] In one particularly preferred embodiment, the compound of Formula IA is a compound wherein X is selected from the group consisting of a bond, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, pentenyl, and heterocycloalkyl;

[0065] wherein Z is selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyano, and haloalkyl;

[0066] wherein R^1 is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, pentenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, phenylethyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl,

isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl, or where R^1 and R^2 together with the atoms to which they are attached form pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, or oxazolidinyl, or where R^1 and R^{1a} together with the atoms to which they are attached form a cyclic moiety selected from the group consisting of piperidinonyl, dihydropyridinonyl, pyridinonyl, dihydroindolonyl, octahydroindolonyl, dihydroisoindolonyl, octahydroisoindolonyl, isoquinolinonyl, dihydroisoquinolinonyl, quinolinonyl, dihydroquinolinonyl, pyrrolidinonyl, and pyrazolidinonyl;

[0067] wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-methylamino, N-ethylamino, N-propylamino, N,N-dimethylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N,N-diethylamino, N-ethyl-N-propylamino, N,N-dipropylamino, N-phenylamino, N-biphenylamino, N-naphthylamino, N-methyl-N-phenylamino, N-ethyl-N-phenylamino, N-propyl-N-phenylamino, N-hydroxyamino, N-methyl-N-hydroxyamino, N-ethyl-N-hydroxyamino, N-propyl-N-hydroxyamino, N-phenyl-N-hydroxyamino, N-biphenyl-N-hydroxyamino, N-naphthyl-N-hydroxyamino, chloro, fluoro, bromo, iodo, cyano, keto, hydroxyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, ethenyl, propenyl, butenyl, pentenyl ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, phenyl, biphenyl, naphthyl, indenyl, phenoxy, biphenoxy, naphthyloxy, indenyloxy, benzyl, phenylethyl, benzylcarbonyl, phenylethylcarbonyl, benzylcarbonylamino, phenylethylcarbonylamino, pyridinylcarbonyl, benzothiophenylcarbonyl, indolylcarbonyl, isoquinolinylcarbonyl, quinolinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl, pyrazolylcarbonyl, imidazolylcarbonyl, isoxazolylcarbonyl, oxazolylcarbonyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, phenoxycarbonyl, biphenoxycarbonyl, naphthyloxycarbonyl, indenyloxycarbonyl, carboxyl, methoxymethoxycarbonyl, methoxyethoxycarbonyl, ethoxymethoxycarbonyl, ethoxyethoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, piperidinylmethyl, piperidinylethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrazolidinylmethyl, pyrazolidinylethyl, imidazolidinylmethyl, imidazolidinylethyl, isoxazolidinylmethyl, isoxazolidinylethyl, oxazolidinylmethyl, oxazolidinylethyl, thiol, oxidosulfanyl, sulfino, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cyclopropylsulfinyl, cyclobutylsulfinyl, cyclopentylsulfinyl, cyclohexylsulfinyl, cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl, phenylthio, biphenylthio, naphthylthio, phenylsulfinyl, biphenylsulfinyl, naphthylsulfinyl, phenylsulfonyl, biphenylsulfonyl, naphthylsulfonyl, piperidinylthio, pyrrolidinylthio, pyrazolidinylthio, imidazolidinylthio, isoxazolidinylthio, oxazolidinylthio, piperidinylsulfinyl, pyrrolidinylsulfinyl, pyrazolidinylsulfinyl, imidazolidinylsulfinyl, isoxazolidinylsulfinyl, oxazolidinylsulfinyl, piperidinylsulfonyl, pyrrolidinylsulfonyl, pyrazolidinylsulfonyl, imidazolidinylsulfonyl, isoxazolidinylsulfonyl, oxazolidinylsulfonyl,

pyridinylthio, benzothiophenylthio, indolylthio, isoquinolinylthio, quinolinylthio, thienylthio, pyrrolylthio, furylthio, pyrazolylthio, imidazolylthio, isoxazolylthio, oxazolylthio, isoindoledionylthio, pyridinylsulfinyl, benzothiophenylsulfinyl, indolylsulfinyl, isoquinolinylsulfinyl, quinolinylsulfinyl, thienylsulfinyl, pyrrolylsulfinyl, furylsulfinyl, pyrazolylsulfinyl, imidazolylsulfinyl, isoxazolylsulfinyl, oxazolylsulfinyl, isoindoledionylsulfinyl, pyridinylsulfonyl, benzothiophenylsulfonyl, indolylsulfonyl, isoquinolinylsulfonyl, quinolinylsulfonyl, thienylsulfonyl, pyrrolylsulfonyl, furylsulfonyl, pyrazolylsulfonyl, imidazolylsulfonyl, isoxazolylsulfonyl, oxazolylsulfonyl, and isoindoledionylsulfonyl;

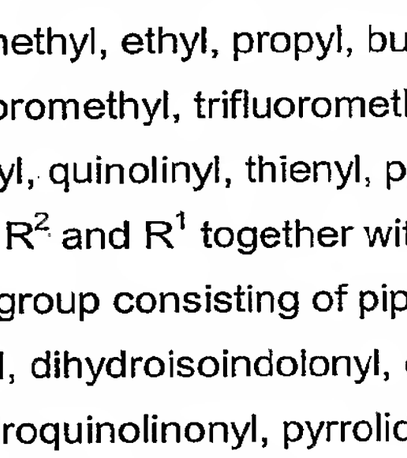
[0068] wherein R^{1a} is selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl, or where R^{1a} and R^1 together with the nitrogen to which they are attached form pyridine, piperidine, indole, indoline, isoindole, isoindolinyl, isoquinoline, quinoline, pyrrole, pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, isoxazole, isoxazolidine, oxazole, or oxazolidine;

[0069] wherein R^2 is selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, or R^2 and R^1 together with the atoms to which they are attached form a cyclic moiety selected from the group consisting of piperidinonyl, dihydropyridinonyl, pyridinonyl, dihydroindolonyl, octahydroindolonyl, dihydroisoindolonyl, octahydroisoindolonyl, isoquinolinonyl, dihydroisoquinolinonyl, quinolinonyl, dihydroquinolinonyl, pyrrolidinonyl, and pyrazolidinonyl;

[0070] wherein R^3 is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and $-NR^7R^8$; and

[0071] wherein R^4, R^5, R^6, R^7, and R^8 are independently selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl.

[0072] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula IIA:



[0073] IIA

[0074] wherein Z is selected from the group consisting of hydrido, halo, alkyl, cyano, and haloalkyl;

[0075] wherein R^9 is selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, or where R^9 and R^{10} together with the atoms to which they are attached form a heterocyclic moiety;

[0076] wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-alkylamino, N,N-dialkylamino, N-arylamino, N-alkyl-N-arylamino, N-hydroxyamino, N-alkyl-N-hydroxyamino, N-aryl-N-hydroxyamino, halo, cyano, keto, hydroxyl, alkyl, haloalkyl, cycloalkyl, alkoxy, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, alkoxycarbonyl, aryloxycarbonyl, carboxyl, alkoxyalkoxycarbonyl, alkoxycarbonylamino, heterocycloalkyl, heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloalkylthio, cycloalkylsulfinyl, cycloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heterocycloalkylthio, heterocycloalkylsulfinyl, heterocycloalkylsulfonyl, heteroarylthio, heteroarylsulfinyl, and heteroarylsulfonyl;

[0077] wherein R^{10} is selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl, or R^{10} and R^9 together with the atoms to which they are attached form a heterocyclic moiety;

[0078] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

[0079] or a pharmaceutically acceptable salt thereof.

[0080] In one preferred embodiment, the compound of Formula IIA is a compound wherein Z is selected from the group consisting of hydrido, halo, C_{1-6} alkyl, cyano, and C_{1-6} haloalkyl;

[0081] wherein R^9 is selected from the group consisting of C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{2-6} alkenyl, C_{3-12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{3-12} aryl, C_{4-18} aralkyl, 3- to 12-membered heteroaryl, and 4- to 18-membered heteroaralkyl, or where R^9 and R^{10} together with the atoms to which they are attached form a 3- to 12-membered heterocyclic moiety;

[0082] wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{3-12} aryl)amino, N-(C_{1-6} alkyl)-N-(C_{3-12} aryl)amino, N-hydroxyamino, N-(C_{1-6} alkyl)-N-hydroxyamino, N-(C_{3-12} aryl)-N-hydroxyamino, halo, cyano, keto, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkenyloxy, C_{3-12} aryl, C_{3-12} aryloxy, C_{4-20} aralkyl, C_{4-20} aralkylcarbonyl, C_{4-20} aralkylcarbonylamino, 3- to 14-membered heteroarylcarbonyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 3- to 12-membered heteroaryl, C_{2-7} alkoxycarbonyl, C_{3-12} aryloxycarbonyl, carboxyl, C_{2-15} alkoxyalkoxycarbonyl, C_{2-7} alkoxycarbonylamino, 3- to 12-membered heterocycloalkyl, 4- to 18-membered heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{3-12} cycloalkylthio, C_{3-12} cycloalkylsulfinyl, C_{3-12} cycloalkylsulfonyl, C_{3-12} arylthio, C_{3-12} arylsulfinyl, C_{3-12} arylsulfonyl, 3- to 12-membered heterocycloalkylthio, 3- to 12-membered heterocycloalkylsulfinyl, 3- to 12-membered heterocycloalkylsulfonyl, 3- to 12-membered heteroarylthio, 3- to 12-membered heteroarylsulfinyl, and 3- to 12-membered heteroarylsulfonyl;

[0083] wherein R^{10} is selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl, or R^{10} and R^9 together with the atoms to which they are attached form a 3- to 12-membered heterocyclic moiety;

[0084] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl.

[0085] In one particularly preferred embodiment, the compound of Formula IIA is a compound wherein Z is selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyano, and haloalkyl;

[0086] wherein R^9 is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, pentenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, phenylethyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl, or where R^9 and R^{10} together with the atoms to which they are attached form pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, or oxazolidinyl;

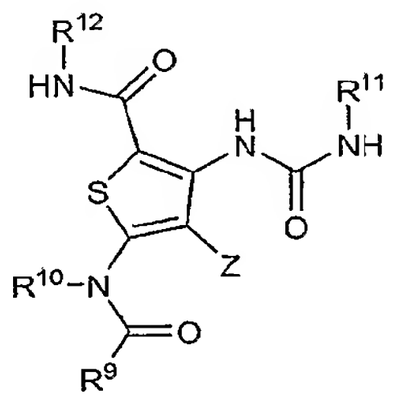
[0087] wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-methylamino, N-ethylamino, N-propylamino, N,N-dimethylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N,N-diethylamino, N-ethyl-N-propylamino, N,N-dipropylamino, N-phenylamino, N-biphenylamino, N-naphthylamino, N-methyl-N-phenylamino, N-ethyl-N-phenylamino, N-propyl-N-phenylamino, N-hydroxyamino, N-methyl-N-hydroxyamino, N-ethyl-N-hydroxyamino, N-propyl-N-hydroxyamino, N-phenyl-N-hydroxyamino, N-biphenyl-N-hydroxyamino, N-naphthyl-N-hydroxyamino, chloro, fluoro, bromo, iodo, cyano, keto, hydroxyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, ethenyl, propenyl, butenyl, pentenyl ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, phenyl, biphenyl, naphthyl, indenyl, phenoxy, biphenoxy, naphthyloxy, indenyloxy, benzyl, phenylethyl, benzylcarbonyl, phenylethylcarbonyl, benzylcarbonylamino, phenylethylcarbonylamino, pyridinylcarbonyl, benzothiophenylcarbonyl, indolylcarbonyl, isoquinolinylcarbonyl, quinolinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl, pyrazolylcarbonyl, imidazolylcarbonyl, isoxazolylcarbonyl, oxazolylcarbonyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, phenoxycarbonyl, biphenoxycarbonyl, naphthyloxycarbonyl, indenyloxycarbonyl, carboxyl, methoxymethoxycarbonyl, methoxyethoxycarbonyl, ethoxymethoxycarbonyl, ethoxyethoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, piperidinylmethyl, piperidinylethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrazolidinylmethyl, pyrazolidinylethyl, imidazolidinylmethyl, imidazolidinylethyl, isoxazolidinylmethyl, isoxazolidinylethyl, oxazolidinylmethyl, oxazolidinylethyl, thiol, oxidosulfanyl, sulfino, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl,

ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cyclopropylsulfinyl, cyclobutylsulfinyl, cyclopentylsulfinyl, cyclohexylsulfinyl, cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl, phenylthio, biphenylthio, naphthylthio, phenylsulfinyl, biphenylsulfinyl, naphthylsulfinyl, phenylsulfonyl, biphenylsulfonyl, naphthylsulfonyl, piperidinylthio, pyrrolidinylthio, pyrazolidinylthio, imidazolidinylthio, isoxazolidinylthio, oxazolidinylthio, piperidinylsulfinyl, pyrrolidinylsulfinyl, pyrazolidinylsulfinyl, imidazolidinylsulfinyl, isoxazolidinylsulfinyl, oxazolidinylsulfinyl, piperidinylsulfonyl, pyrrolidinylsulfonyl, pyrazolidinylsulfonyl, imidazolidinylsulfonyl, isoxazolidinylsulfonyl, oxazolidinylsulfonyl, pyridinylthio, benzothiophenylthio, indolylthio, isoquinolinylthio, quinolinylthio, thienylthio, pyrrolylthio, furylthio, pyrazolylthio, imidazolylthio, isoxazolylthio, oxazolylthio, isoindoledionylthio, pyridinylsulfinyl, benzothiophenylsulfinyl, indolylsulfinyl, isoquinolinylsulfinyl, quinolinylsulfinyl, thienylsulfinyl, pyrrolylsulfinyl, furylsulfinyl, pyrazolylsulfinyl, imidazolylsulfinyl, isoxazolylsulfinyl, oxazolylsulfinyl, isoindoledionylsulfinyl, pyridinylsulfonyl, benzothiophenylsulfonyl, indolylsulfonyl, isoquinolinylsulfonyl, quinolinylsulfonyl, thienylsulfonyl, pyrrolylsulfonyl, furylsulfonyl, pyrazolylsulfonyl, imidazolylsulfonyl, isoxazolylsulfonyl, oxazolylsulfonyl, and isoindoledionylsulfonyl;

[0088] wherein R^{10} is selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, or R^{10} and R^9 together with the atoms to which they are attached form a cyclic moiety selected from the group consisting of piperidinonyl, dihydropyridinonyl, pyridinonyl, dihydroindolonyl, octahydroindolonyl, dihydroisoindolonyl, octahydroisoindolonyl, isoquinolinonyl, dihydroisoquinolinonyl, quinolinonyl, dihydroquinolinonyl, pyrrolidinonyl, and pyrazolidinonyl;

[0089] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl.

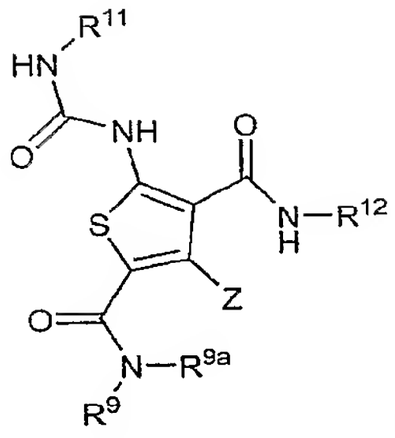
[0090] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula IIB:



[0091] IIB

[0092] wherein Z, R^9, R^{10}, R^{11}, and R^{12} are as defined above for Formula IIA; or a pharmaceutically acceptable salt thereof.

[0093] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula IIC:



[0094] IIC

[0095] wherein Z is selected from the group consisting of hydrido, halo, alkyl, cyano, and haloalkyl;

[0096] wherein R^9 is selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, or where R^9 and R^{9a} together with the nitrogen to which they are attached form a heterocyclic moiety;

[0097] wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-alkylamino, N,N-dialkylamino, N-arylamino, N-alkyl-N-arylamino, N-hydroxyamino, N-alkyl-N-hydroxyamino, N-aryl-N-hydroxyamino, halo, cyano, keto, hydroxyl, alkyl, haloalkyl, cycloalkyl, alkoxy, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, alkoxycarbonyl, aryloxycarbonyl, carboxyl, alkoxyalkoxycarbonyl, alkoxycarbonylamino, heterocycloalkyl, heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloalkylthio, cycloalkylsulfinyl, cycloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heterocycloalkylthio, heterocycloalkylsulfinyl, heterocycloalkylsulfonyl, heteroarylthio, heteroarylsulfinyl, and heteroarylsulfonyl;

[0098] wherein R^{9a} is selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl, or where R^{9a} and R^9 together with the nitrogen to which they are attached form a heterocyclic moiety;

[0099] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

[00100] or a pharmaceutically acceptable salt thereof.

[00101] In one preferred embodiment, the compound of Formula IIC is a compound wherein Z is selected from the group consisting of hydrido, halo, C_{1-6} alkyl, cyano, and C_{1-6} haloalkyl;

[00102] wherein R^9 is selected from the group consisting of C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{2-6} alkenyl, C_{3-12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{3-12} aryl, C_{4-18} aralkyl, 3- to 12-membered heteroaryl, and 4- to 18-membered heteroaralkyl, or where R^9 and R^{9a} together with the nitrogen to which they are attached form a 3- to 12-membered heterocyclic moiety;

[00103] wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{3-12} aryl)amino, N-(C_{1-6} alkyl)-N-(C_{3-12} aryl)amino, N-hydroxyamino, N-(C_{1-6} alkyl)-N-hydroxyamino, N-(C_{3-12} aryl)-N-hydroxyamino, halo, cyano, keto, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkenyloxy, C_{3-12} aryl, C_{3-12} aryloxy, C_{4-20} aralkyl, C_{4-20} aralkylcarbonyl, C_{4-20} aralkylcarbonylamino, 3- to 14-membered heteroarylcarbonyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 3- to 12-membered heteroaryl, C_{2-7} alkoxycarbonyl, C_{3-12} aryloxycarbonyl, carboxyl, C_{2-15} alkoxyalkoxycarbonyl, C_{2-7} alkoxycarbonylamino, 3- to 12-membered heterocycloalkyl, 4- to 18-membered heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, C_{1-6} alkylthio, C_{1-6}

alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{3-12} cycloalkylthio, C_{3-12} cycloalkylsulfinyl, C_{3-12} cycloalkylsulfonyl, C_{3-12} arylthio, C_{3-12} arylsulfinyl, C_{3-12} arylsulfonyl, 3- to 12-membered heterocycloalkylthio, 3- to 12-membered heterocycloalkylsulfinyl, 3- to 12-membered heterocycloalkylsulfonyl, 3- to 12-membered heteroarylthio, 3- to 12-membered heteroarylsulfinyl, and 3- to 12-membered heteroarylsulfonyl;

[00104] wherein R^{9a} is selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl, or where R^{9a} and R^9 together with the nitrogen to which they are attached form a 3- to 12-membered heterocyclic moiety;

[00105] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl.

[00106] In one particularly preferred embodiment, the compound of Formula IIC is a compound wherein Z is selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyano, and haloalkyl;

[00107] wherein R^9 is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, pentenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, phenylethyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl, or where R^9 and R^{9a} together with the atoms to which they are attached form a cyclic moiety selected from the group consisting of piperidinonyl, dihydropyridinonyl, pyridinonyl, dihydroindolonyl, octahydroindolonyl, dihydroisoindolonyl, octahydroisoindolonyl, isoquinolinonyl, dihydroisoquinolinonyl, quinolinonyl, dihydroquinolinonyl, pyrrolidinonyl, and pyrazolidinonyl;

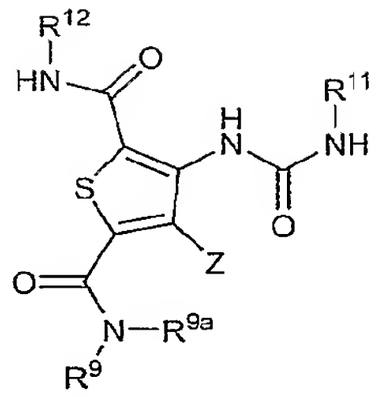
[00108] wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-methylamino, N-ethylamino, N-propylamino, N,N-dimethylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N,N-diethylamino, N-ethyl-N-propylamino, N,N-dipropylamino, N-phenylamino, N-biphenylamino, N-naphthylamino, N-methyl-N-phenylamino, N-ethyl-N-phenylamino, N-propyl-N-phenylamino, N-hydroxyamino, N-methyl-N-hydroxyamino, N-ethyl-N-hydroxyamino, N-propyl-N-hydroxyamino, N-phenyl-N-hydroxyamino, N-biphenyl-N-hydroxyamino, N-naphthyl-N-hydroxyamino, chloro, fluoro, bromo, iodo, cyano, keto, hydroxyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, ethenyl, propenyl, butenyl, pentenyl ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, phenyl, biphenyl, naphthyl, indenyl, phenoxy, biphenoxy, naphthyloxy, indenyloxy, benzyl, phenylethyl, benzylcarbonyl, phenylethylcarbonyl, benzylcarbonylamino, phenylethylcarbonylamino, pyridinylcarbonyl, benzothiophenylcarbonyl, indolylcarbonyl, isoquinolinylcarbonyl, quinolinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl, pyrazolylcarbonyl, imidazolylcarbonyl, isoxazolylcarbonyl, oxazolylcarbonyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl,

isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, phenoxycarbonyl, biphenoxycarbonyl, naphthyloxycarbonyl, indenyloxycarbonyl, carboxyl, methoxymethoxycarbonyl, methoxyethoxycarbonyl, ethoxymethoxycarbonyl, ethoxyethoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, piperidinylmethyl, piperidinylethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrazolidinylmethyl, pyrazolidinylethyl, imidazolidinylmethyl, imidazolidinylethyl, isoxazolidinylmethyl, isoxazolidinylethyl, oxazolidinylmethyl, oxazolidinylethyl, thiol, oxidosulfanyl, sulfino, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cyclopropylsulfinyl, cyclobutylsulfinyl, cyclopentylsulfinyl, cyclohexylsulfinyl, cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl, phenylthio, biphenylthio, naphthylthio, phenylsulfinyl, biphenylsulfinyl, naphthylsulfinyl, phenylsulfonyl, biphenylsulfonyl, naphthylsulfonyl, piperidinylthio, pyrrolidinylthio, pyrazolidinylthio, imidazolidinylthio, isoxazolidinylthio, oxazolidinylthio, piperidinylsulfinyl, pyrrolidinylsulfinyl, pyrazolidinylsulfinyl, imidazolidinylsulfinyl, isoxazolidinylsulfinyl, oxazolidinylsulfinyl, piperidinylsulfonyl, pyrrolidinylsulfonyl, pyrazolidinylsulfonyl, imidazolidinylsulfonyl, isoxazolidinylsulfonyl, oxazolidinylsulfonyl, pyridinylthio, benzothiophenylthio, indolylthio, isoquinolinylthio, quinolinylthio, thienylthio, pyrrolylthio, furylthio, pyrazolylthio, imidazolylthio, isoxazolylthio, oxazolylthio, isoindoledionylthio, pyridinylsulfinyl, benzothiophenylsulfinyl, indolylsulfinyl, isoquinolinylsulfinyl, quinolinylsulfinyl, thienylsulfinyl, pyrrolylsulfinyl, furylsulfinyl, pyrazolylsulfinyl, imidazolylsulfinyl, isoxazolylsulfinyl, oxazolylsulfinyl, isoindoledionylsulfinyl, pyridinylsulfonyl, benzothiophenylsulfonyl, indolylsulfonyl, isoquinolinylsulfonyl, quinolinylsulfonyl, thienylsulfonyl, pyrrolylsulfonyl, furylsulfonyl, pyrazolylsulfonyl, imidazolylsulfonyl, isoxazolylsulfonyl, oxazolylsulfonyl, and isoindoledionylsulfonyl;

[00109] wherein R^{9a} is selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl, or where R^{9a} and R^{9} together with the nitrogen to which they are attached form pyridine, piperidine, indole, indoline, isoindole, isoindolinyl, isoquinoline, quinoline, pyrrole, pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, isoxazole, isoxazolidine, oxazole, or oxazolidine;

[00110] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl.

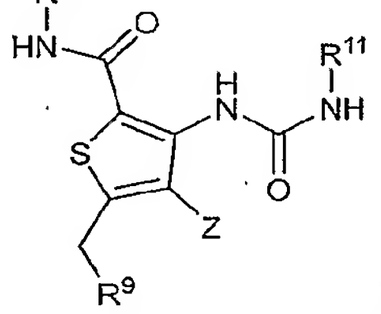
[00111] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula IID:



[00112] IID

[00113] wherein Z, R^9, R^{9a}, R^{11}, and R^{12} are as defined above for Formula IIC; or a pharmaceutically acceptable salt thereof.

[00114] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula IIE:



[00115] IIE

[00116] wherein Z is selected from the group consisting of hydrido, halo, alkyl, cyano, and haloalkyl;

[00117] wherein R^1 is selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

[00118] wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-alkylamino, N,N-dialkylamino, N-arylamino, N-alkyl-N-arylamino, N-hydroxyamino, N-alkyl-N-hydroxyamino, N-aryl-N-hydroxyamino, halo, cyano, keto, hydroxyl, alkyl, haloalkyl, cycloalkyl, alkoxy, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, alkoxycarbonyl, aryloxycarbonyl, carboxyl, alkoxyalkoxycarbonyl, alkoxycarbonylamino, heterocycloalkyl, heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloalkylthio, cycloalkylsulfinyl, cycloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heterocycloalkylthio, heterocycloalkylsulfinyl, heterocycloalkylsulfonyl, heteroarylthio, heteroarylsulfinyl, and heteroarylsulfonyl;

[00119] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

[00120] or a pharmaceutically acceptable salt thereof.

[00121] In one preferred embodiment, the compound of Formula IIE is a compound wherein Z is selected from the group consisting of hydrido, halo, C_{1-6} alkyl, cyano, and C_{1-6} haloalkyl;

[00122] wherein R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{2-6} alkenyl, C_{3-12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{3-12} aryl, C_{4-18} aralkyl, 3- to 12-membered heteroaryl, and 4- to 18-membered heteroaralkyl;

[00123] wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{3-12} aryl)amino, N-(C_{1-6} alkyl)-N-(C_{3-12} aryl)amino, N-hydroxyamino, N-(C_{1-6} alkyl)-N-hydroxyamino, N-(C_{3-12} aryl)-N-hydroxyamino, halo, cyano, keto, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkenyloxy, C_{3-12} aryl, C_{3-12} aryloxy, C_{4-20} aralkyl, C_{4-20} aralkylcarbonyl, C_{4-20}

aralkylcarbonylamino, 3- to 14-membered heteroarylcarbonyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 3- to 12-membered heteroaryl, C_{2-7} alkoxycarbonyl, C_{3-12} aryloxycarbonyl, carboxyl, C_{2-15} alkoxyalkoxycarbonyl, C_{2-7} alkoxycarbonylamino, 3- to 12-membered heterocycloalkyl, 4- to 18-membered heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{3-12} cycloalkylthio, C_{3-12} cycloalkylsulfinyl, C_{3-12} cycloalkylsulfonyl, C_{3-12} arylthio, C_{3-12} arylsulfinyl, C_{3-12} arylsulfonyl, 3- to 12-membered heterocycloalkylthio, 3- to 12-membered heterocycloalkylsulfinyl, 3- to 12-membered heterocycloalkylsulfonyl, 3- to 12-membered heteroarylthio, 3- to 12-membered heteroarylsulfinyl, and 3- to 12-membered heteroarylsulfonyl;

[00124] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl.

[00125] In one particularly preferred embodiment, the compound of Formula IIE is a compound wherein Z is selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyano, and haloalkyl;

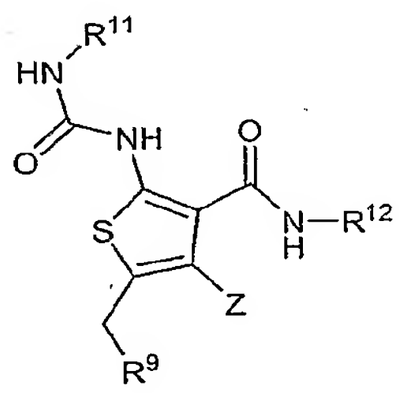
[00126] wherein R^1 is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, pentenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, phenylethyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl; isoindoledionyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl;

[00127] wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-methylamino, N-ethylamino, N-propylamino, N,N-dimethylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N,N-diethylamino, N-ethyl-N-propylamino, N,N-dipropylamino, N-phenylamino, N-biphenylamino, N-naphthylamino, N-methyl-N-phenylamino, N-ethyl-N-phenylamino, N-propyl-N-phenylamino, N-hydroxyamino, N-methyl-N-hydroxyamino, N-ethyl-N-hydroxyamino, N-propyl-N-hydroxyamino, N-phenyl-N-hydroxyamino, N-biphenyl-N-hydroxyamino, N-naphthyl-N-hydroxyamino, chloro, fluoro, bromo, iodo, cyano, keto, hydroxyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, ethenyl, propenyl, butenyl, pentenyl ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, phenyl, biphenyl, naphthyl, indenyl, phenoxy, biphenoxy, naphthyloxy, indenyloxy, benzyl, phenylethyl, benzylcarbonyl, phenylethylcarbonyl, benzylcarbonylamino, phenylethylcarbonylamino, pyridinylcarbonyl, benzothiophenylcarbonyl, indolylcarbonyl, isoquinolinylcarbonyl, quinolinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl, pyrazolylcarbonyl, imidazolylcarbonyl, isoxazolylcarbonyl, oxazolylcarbonyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, phenoxycarbonyl, biphenoxycarbonyl, naphthyloxycarbonyl, indenyloxycarbonyl, carboxyl,

methoxymethoxycarbonyl, methoxyethoxycarbonyl, ethoxymethoxycarbonyl, ethoxyethoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, piperidinylmethyl, piperidinylethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrazolidinylmethyl, pyrazolidinylethyl, imidazolidinylmethyl, imidazolidinylethyl, isoxazolidinylmethyl, isoxazolidinylethyl, oxazolidinylmethyl, oxazolidinylethyl, thiol, oxidosulfanyl, sulfino, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cyclopropylsulfinyl, cyclobutylsulfinyl, cyclopentylsulfinyl, cyclohexylsulfinyl, cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl, phenylthio, biphenylthio, naphthylthio, phenylsulfinyl, biphenylsulfinyl, naphthylsulfinyl, phenylsulfonyl, biphenylsulfonyl, naphthylsulfonyl, piperidinylthio, pyrrolidinylthio, pyrazolidinylthio, imidazolidinylthio, isoxazolidinylthio, oxazolidinylthio, piperidinylsulfinyl, pyrrolidinylsulfinyl, pyrazolidinylsulfinyl, imidazolidinylsulfinyl, isoxazolidinylsulfinyl, oxazolidinylsulfinyl, piperidinylsulfonyl, pyrrolidinylsulfonyl, pyrazolidinylsulfonyl, imidazolidinylsulfonyl, isoxazolidinylsulfonyl, oxazolidinylsulfonyl, pyridinylthio, benzothiophenylthio, indolylthio, isoquinolinylthio, quinolinylthio, thienylthio, pyrrolylthio, furylthio, pyrazolylthio, imidazolylthio, isoxazolylthio, oxazolylthio, isoindoledionylthio, pyridinylsulfinyl, benzothiophenylsulfinyl, indolylsulfinyl, isoquinolinylsulfinyl, quinolinylsulfinyl, thienylsulfinyl, pyrrolylsulfinyl, furylsulfinyl, pyrazolylsulfinyl, imidazolylsulfinyl, isoxazolylsulfinyl, oxazolylsulfinyl, isoindoledionylsulfinyl, pyridinylsulfonyl, benzothiophenylsulfonyl, indolylsulfonyl, isoquinolinylsulfonyl, quinolinylsulfonyl, thienylsulfonyl, pyrrolylsulfonyl, furylsulfonyl, pyrazolylsulfonyl, imidazolylsulfonyl, isoxazolylsulfonyl, oxazolylsulfonyl, and isoindoledionylsulfonyl;

[00128] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl.

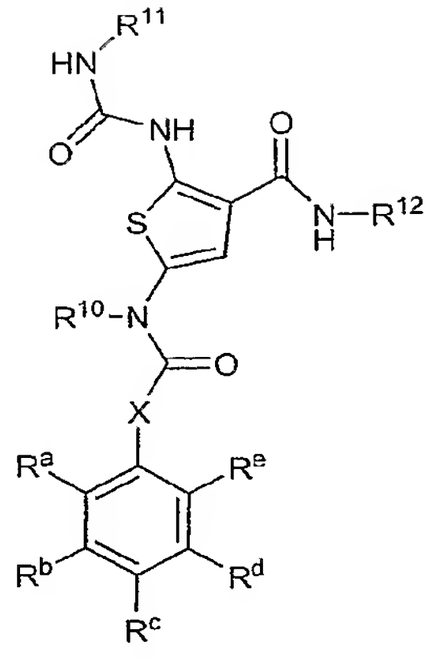
[00129] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula IIF:



[00130] IIF

[00131] wherein Z, R^1, R^{11}, and R^{12} are as defined above for Formula IIE; or a pharmaceutically acceptable salt thereof.

[00132] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula III:



[00133] III

[00134] wherein X is a bond or alkyl;

[00135] wherein R^a is selected from the group consisting of halo, cyano, alkyl, cycloalkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkoxy, alkoxycarbonyl, carboxyl, heterocycloalkylalkyl, and alkylsulfonyl, or wherein R^a and R^{10} together with the atoms to which they are attached form a heterocyclic moiety;

[00136] wherein R^b, R^c, R^d, and R^e are independently selected from the group consisting of halo, cyano, alkyl, cycloalkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkoxy, alkoxycarbonyl, carboxyl, heterocycloalkylalkyl, and alkylsulfonyl;

[00137] wherein R^{10} is selected from the group consisting of hydrido and alkyl, or R^{10} and R^a together with the atoms to which they are attached form a heterocyclic moiety; and

[00138] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and alkyl;

[00139] wherein R^a and R^b, or R^b and R^c, or R^c and R^d, or R^d and R^e may form a ring moiety fused to the phenyl ring to which they are both attached, said ring moiety selected from the group consisting of cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein said ring moiety may be substituted by one or more substituents selected from the group consisting of halo, keto, alkyl, hydroxy, alkoxy, aralkyl, and aralkoxy;

[00140] or a pharmaceutically acceptable salt thereof.

[00141] In one preferred embodiment, the compound of Formula III is a compound wherein X is a bond or C_{1-6} alkyl;

[00142] wherein R^a is selected from the group consisting of halo, cyano, C_{1-6} alkyl, cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-12} aryl, C_{3-12} aryloxy, C_{3-12} aralkoxy, C_{2-6} alkoxycarbonyl, carboxyl, 3- to 18-membered heterocycloalkylalkyl, and C_{1-6} alkylsulfonyl, or wherein R^a and R^{10} together with the atoms to which they are attached form a 3- to 12-membered heterocyclic moiety;

[00143] wherein R^b, R^c, R^d, and R^e are independently selected from the group consisting of halo, cyano, C_{1-6} alkyl, cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-12} aryl, C_{3-12} aryloxy, C_{3-12} aralkoxy, C_{2-6} alkoxycarbonyl, carboxyl, 3- to 18-membered heterocycloalkylalkyl, and C_{1-6} alkylsulfonyl;

[00144] wherein R^{10} is selected from the group consisting of hydrido and C_{1-6} alkyl, or R^{10} and R^a together with the atoms to which they are attached form a 3- to 12-membered heterocyclic moiety; and

[00145] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and C_{1-6} alkyl;

[00146] wherein R^a and R^b, or R^b and R^c, or R^c and R^d, or R^d and R^e may form a ring moiety fused to the phenyl ring to which they are both attached, said ring moiety selected from the group

consisting of C_{3-12} cycloalkyl, C_{3-12} cycloalkenyl, C_{3-12} aryl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, and 3- to 12-membered heteroaryl, wherein said ring moiety may be substituted by one or more substituents selected from the group consisting of halo, keto, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{3-12} aralkyl, and C_{3-12} aralkoxy.

[00147] In one particularly preferred embodiment, the compound of Formula III is a compound wherein X is selected from the group consisting of a bond, methyl, ethyl, and propyl;

[00148] wherein R^a is selected from the group consisting of chloro, fluoro, bromo, cyano, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chloromethyl, trifluoromethyl, methoxy, phenyl, phenoxy, benzyloxy, methoxycarbonyl, carboxyl, piperidinylmethyl, methylsulfonyl, benzyloxyphenyl, and methylpiperazinylmethyl, or wherein R^a and R^{10} together with the atoms to which they are attached form an isoindoledionyl group;

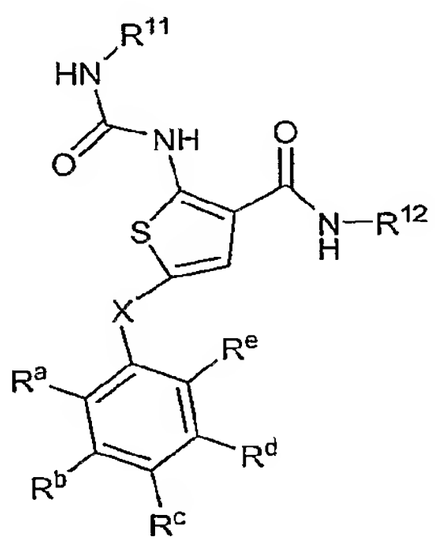
[00149] wherein R^b, R^c, R^d, and R^e are independently selected from the group consisting of chloro, fluoro, bromo, cyano, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chloromethyl, trifluoromethyl, methoxy, phenyl, phenoxy, benzyloxy, methoxycarbonyl, carboxyl, piperidinylmethyl, methylsulfonyl, benzyloxyphenyl, and methylpiperazinylmethyl;

[00150] wherein R^{10} is selected from the group consisting of hydrido and methyl, or R^{10} and R^a together with the atoms to which they are attached form an isoindoledionyl group; and

[00151] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and methyl;

[00152] wherein R^a and R^b, or R^b and R^c, or R^c and R^d, or R^d and R^e may form a ring moiety fused to the phenyl ring to which they are both attached, said ring moiety selected from the group consisting of cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, phenyl, pyridinyl, thienyl, pyrrolyl, furyl, and pyrazolyl, wherein said ring moiety may be substituted by one or more substituents selected from the group consisting of chloro, fluoro, bromo, keto, methyl, methoxy, benzyl, and benzyloxy.

[00153] In another particularly preferred embodiment, the compound of Formula I is a compound of Formula IV:



[00154] IV

[00155] wherein X is alkyl;

[00156] wherein R^a, R^b, R^c, R^d, and R^e are independently selected from the group consisting of halo, cyano, alkyl, haloalkyl, alkoxy, aryl, and aralkoxy; and

[00157] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and alkyl;

[00158] wherein R^a and R^b, or R^b and R^c, or R^c and R^d, or R^d and R^e may form an aryl moiety fused to the phenyl ring to which they are both attached, wherein said aryl moiety may be substituted by one or more substituents selected from the group consisting of halo, alkyl, and alkoxy;

[00159] or a pharmaceutically acceptable salt thereof.

[00160] In one preferred embodiment, the compound of Formula IV is a compound wherein X is C_{1-6} alkyl;

[00161] wherein R^a, R^b, R^c, R^d, and R^e are independently selected from the group consisting of halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-12} aryl, and C_{4-14} aralkoxy; and

[00162] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and C_{1-6} alkyl;

[00163] wherein R^a and R^b, or R^b and R^c, or R^c and R^d, or R^d and R^e may form an C_{3-12} aryl moiety fused to the phenyl ring to which they are both attached, wherein said aryl moiety may be substituted by one or more substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

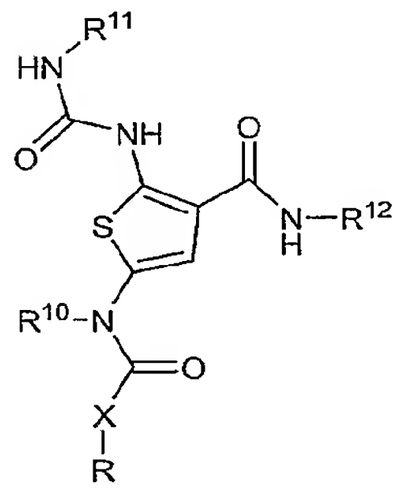
[00164] In one particularly preferred embodiment, the compound of Formula IV is a compound wherein X is selected from the group consisting of methyl, ethyl, and propyl;

[00165] wherein R^a, R^b, R^c, R^d, and R^e are independently selected from the group consisting of chloro, bromo, fluoro, cyano, methyl, trifluoromethyl, methoxy, phenyl, and benzyloxy; and

[00166] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and methyl;

[00167] wherein R^a and R^b, or R^b and R^c, or R^c and R^d, or R^d and R^e, together with the phenyl ring to which they are attached, may form a naphthyl ring, wherein said naphthyl ring may be optionally substituted by one or more substituents selected from the group consisting of bromo, chloro, fluoro, methyl, and methoxy.

[00168] In another particularly preferred embodiment, the compound of Formula I is a compound of Formula V:



V

[00169]

[00170] wherein X is a bond or alkyl;

[00171] wherein R is a 5- to 12-membered heterocyclic moiety;

[00172] wherein R is optionally substituted by one or more substituents independently selected from the group consisting of halo, alkyl, alkoxycarbonyl, carboxyl, and heteroarylalkyl;

[00173] wherein R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrido and alkyl;

[00174] or a pharmaceutically acceptable salt thereof.

[00175] In one preferred embodiment, the compound of Formula V is a compound wherein X is a bond or C_{1-6} alkyl;

[00176] wherein R is optionally substituted by one or more substituents independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-7} alkoxycarbonyl, carboxyl, and 3- to 12-membered heteroarylalkyl;

[00177] wherein R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrido and C_{1-6} alkyl.

[00178] In one particularly preferred embodiment, the compound of Formula V is a compound wherein X is selected from the group consisting of a bond, methyl, ethyl, and propyl;

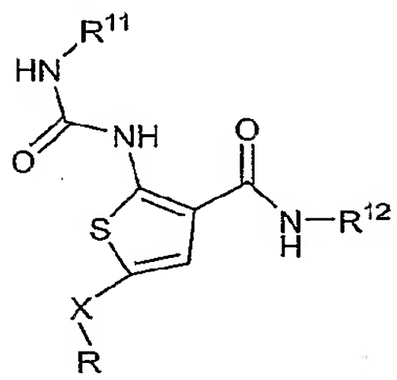
[00179] wherein R is a heterocyclic moiety selected from the group consisting of pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, 7-azabicyclo[2.2.1]heptane, isoindolinyl, piperidinyl, and pyrrolidinyl;

[00180] wherein R is optionally substituted by one or more substituents independently selected from the group consisting of bromo, chloro, fluoro, methyl, methoxycarbonyl, propoxycarbonyl, carboxyl, and pyridinylmethyl;

[00181] wherein R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrido and methyl.

[00182] In another particularly preferred embodiment, the compound of Formula I is a compound of Formula VII:

[00183]



VII

[00184] wherein X is alkyl;

[00185] wherein R is selected from the group consisting of alkyl, alkenyl, C_{3-12} cycloalkyl, and C_{3-12} cycloalkenyl;

[00186] wherein R is optionally substituted by one or more substituents independently selected from the group consisting of cyano, keto, alkyl, alkoxy, haloalkyl, alkylcarbonyl, aryl, cycloalkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, alkoxycarbonyl, carboxyl, and alkoxyalkoxycarbonyl; and

[00187] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and alkyl;

[00188] or a pharmaceutically acceptable salt thereof.

[00189] In one preferred embodiment, the compound of Formula VII is a compound wherein X is C_{1-6} alkyl;

[00190] wherein R is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-12} cycloalkyl, and C_{3-12} cycloalkenyl;

[00191] wherein R is optionally substituted by one or more substituents independently selected from the group consisting of cyano, keto, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{2-7} alkylcarbonyl, C_{3-12} aryl,

C_{3-12} cycloalkyl, C_{4-18} aralkylcarbonyl, C_{4-18} aralkylcarbonylamino, 3- to 12-membered heteroarylcarbonyl, C_{2-7} alkoxycarbonyl, carboxyl, and C_{3-18} alkoxyalkoxycarbonyl; and

[00192] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and C_{1-6} alkyl.

[00193] In one particularly preferred embodiment, the compound of Formula VII is a compound wherein X is selected from the group consisting of methyl, ethyl, and propyl;

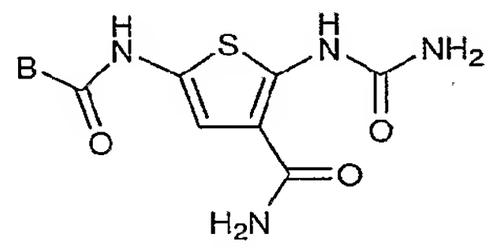
[00194] wherein R is selected from the group consisting of methyl, ethyl, propyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthyl, octahydroindyl, octahydropentalene, bicyclo[2.2.1]heptyl, tricyclo[2.2.1.0~2,6~]heptyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, decahydronaphthenyl, hexahydroindenyl, hexahydropentalenyl, bicyclo[2.2.1]heptenyl, and bicyclo[3.1.1]heptenyl;

[00195] wherein R is optionally substituted by one or more substituents independently selected from the group consisting of cyano, keto, methyl, ethyl, propyl, cyclopentyl, cyclohexyl, trifluoromethyl, methylcarbonyl, propylcarbonyl, pentylcarbonyl, phenyl, benzylcarbonyl, benzylcarbonylamino, thienylcarbonyl, propoxycarbonyl, butoxycarbonyl, carboxyl, and methoxyethoxycarbonyl; and

[00196] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and methyl.

[00197] In a particularly preferred embodiment, the compound of Formula I is selected from the group of compounds consisting of the compounds shown in Tables I, II, III, and IV, below:

Table I



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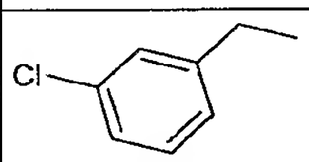
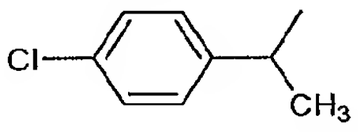
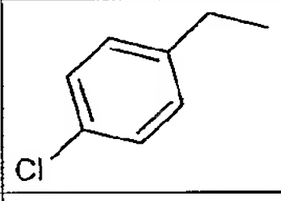
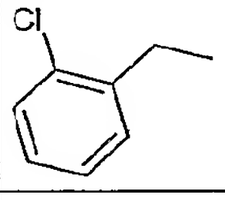
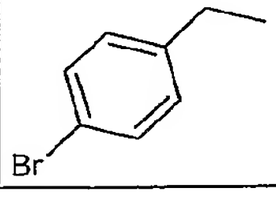
3	
4	
5	
6	
7	

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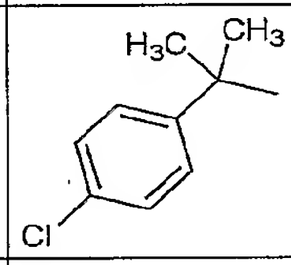
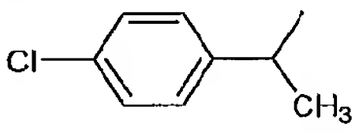
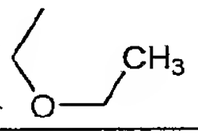
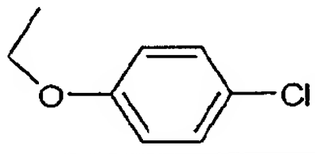
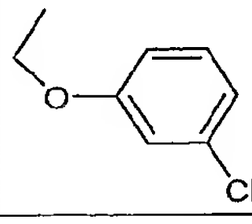
8	
9, 10	
11	
12	
13	

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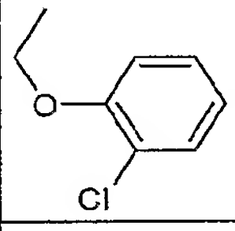
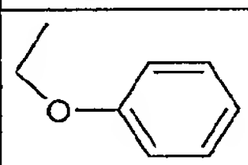
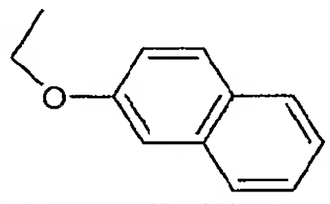
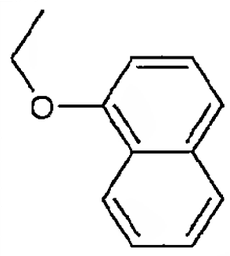
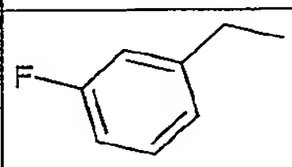
14	
15	
16	
17	
18	

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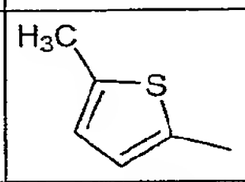
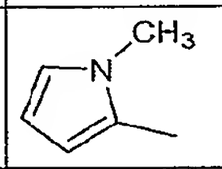
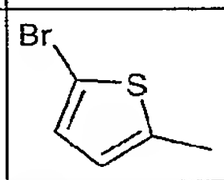
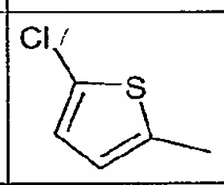
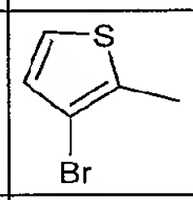
19	
20	
21	
22	
23	
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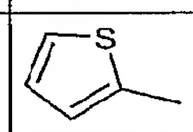
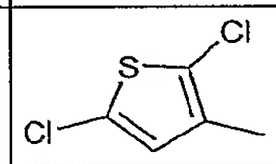
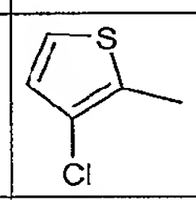
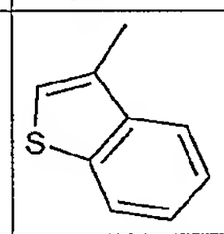
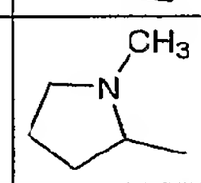
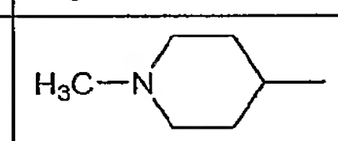
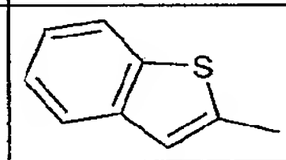
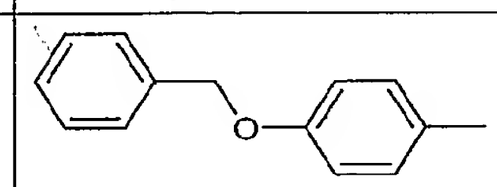
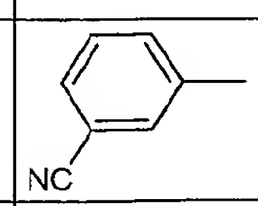
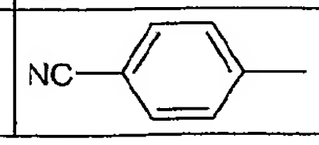
25	
26	
27	
28	
29	
30	
33	
34	
35	
36	

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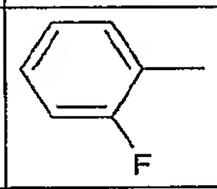
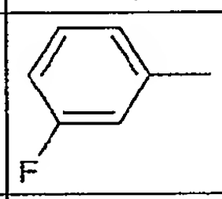
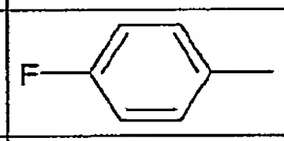
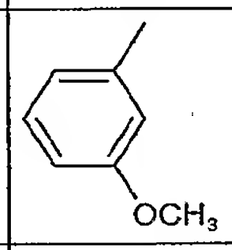
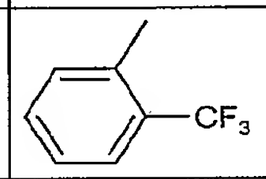
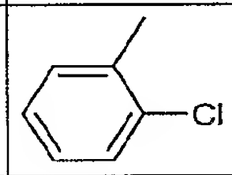
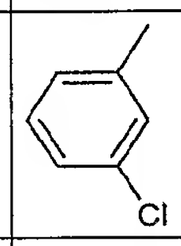
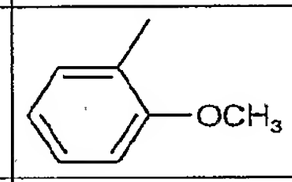
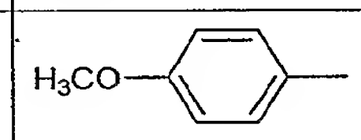
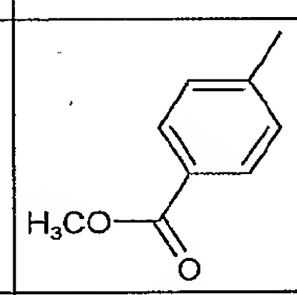
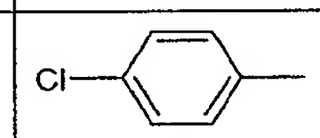
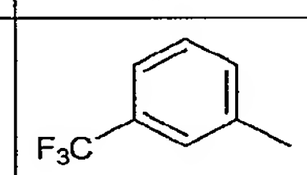
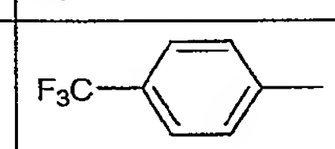
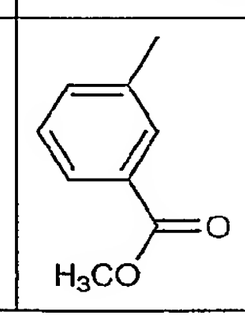
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	

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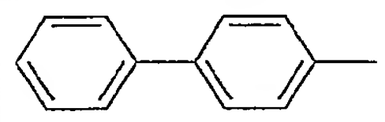
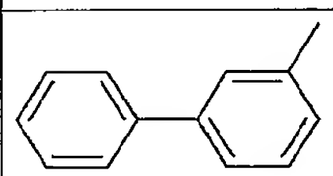
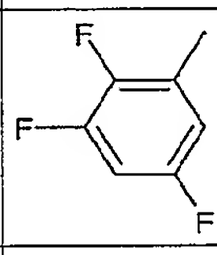
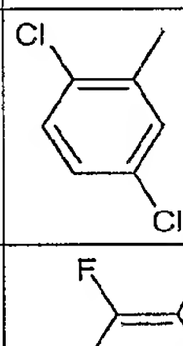
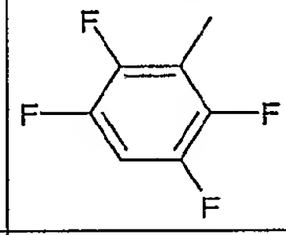
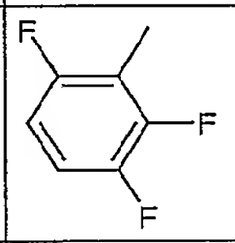
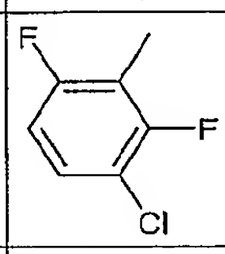
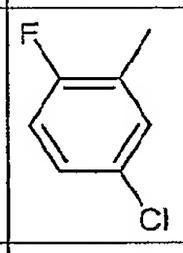
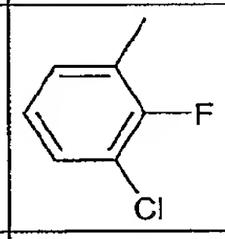
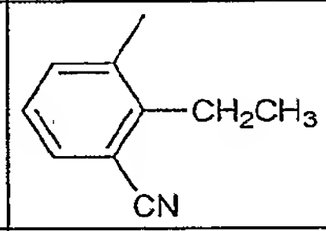
52	
53	
54	
55	
56	
57	
58	
59	
60	
61	
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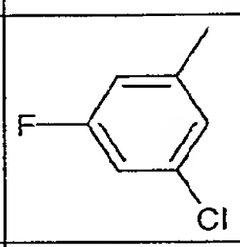
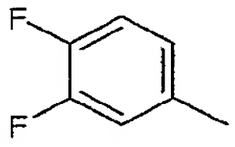
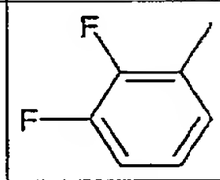
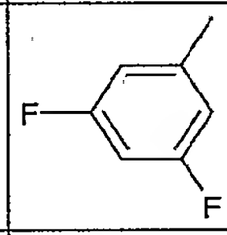
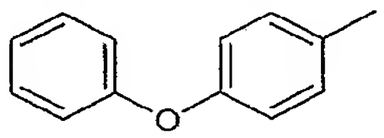
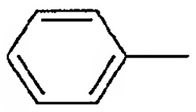
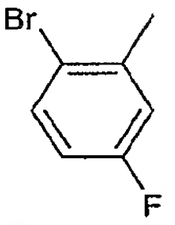
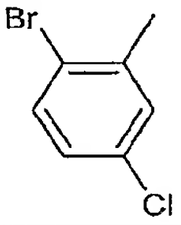
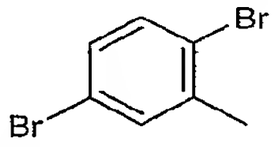
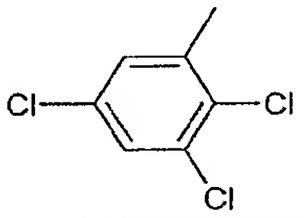
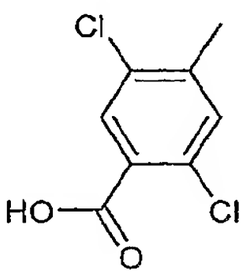
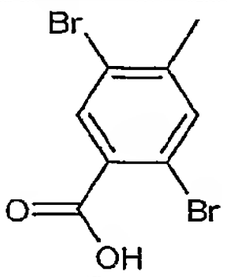
64	
65	
66	
67	
68	
69	
70	
71	
72	
73	
74	
75	

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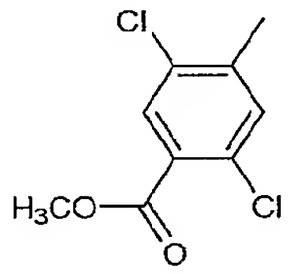
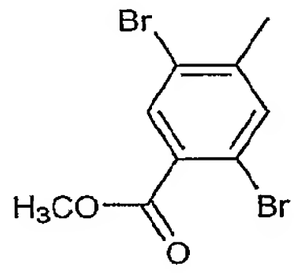
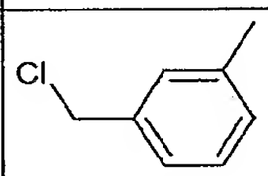
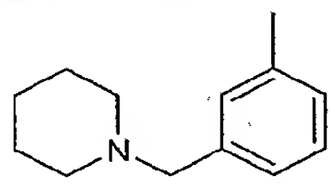
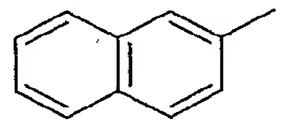
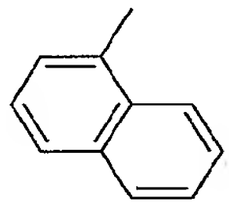
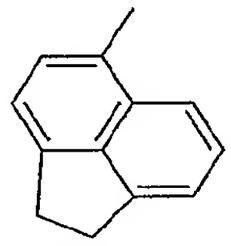
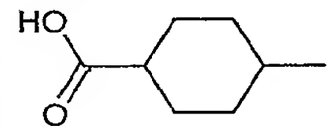
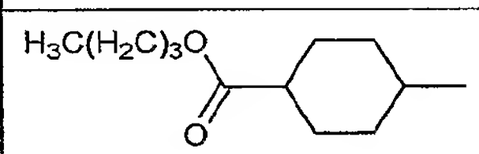
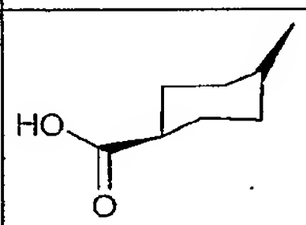
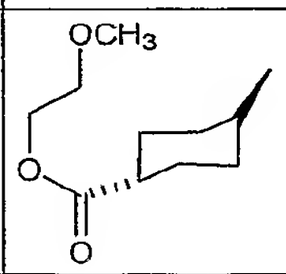
76	
77	
78	
79	
101	
102	
103	
104	
105	
109	
110	

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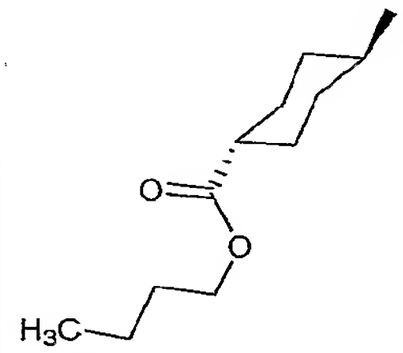
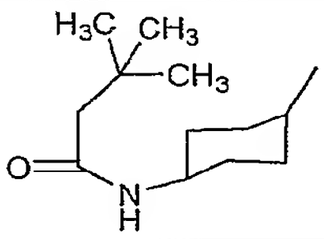
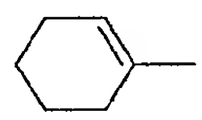
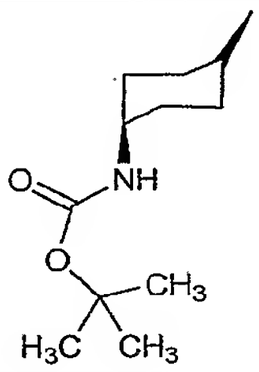
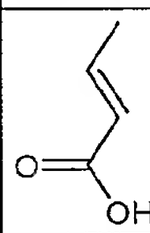
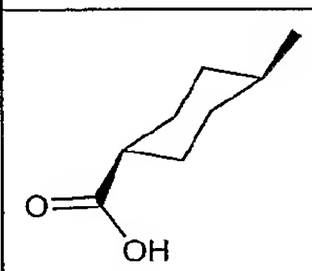
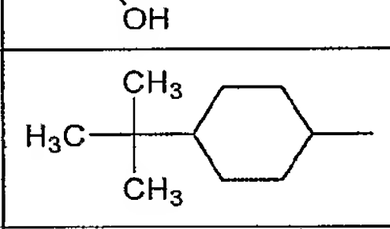
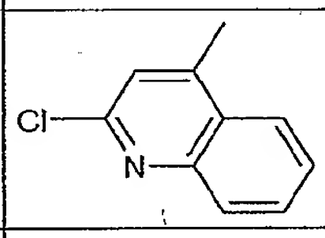
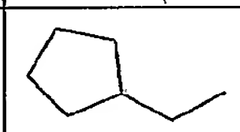
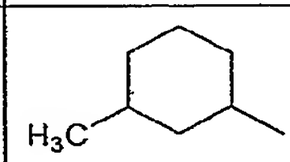
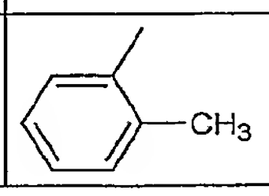
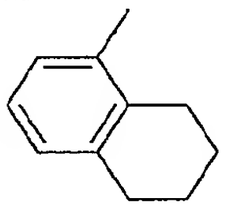
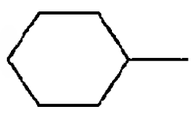
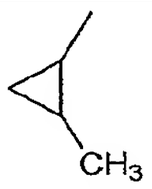
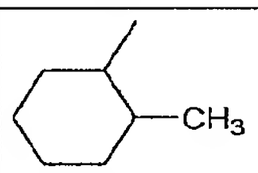
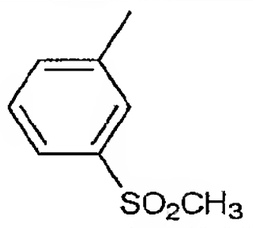
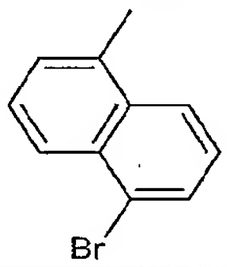
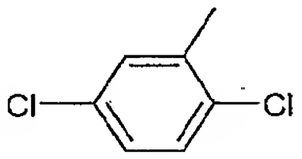
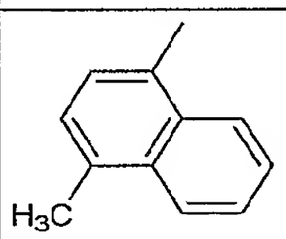
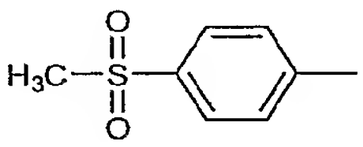
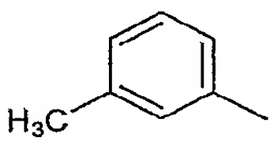
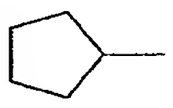
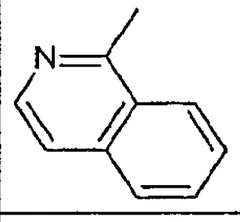
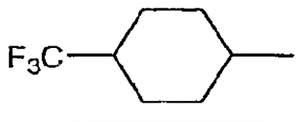
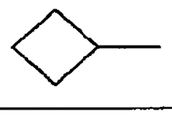
110.1	
111	
112	
113	
114	
115	
116	
117	
118	
119	
120	

Ex.	B-
121	
123	
124	
125	
126	
127	
128	
129	
130	
131	
132	
133	
134	
135	

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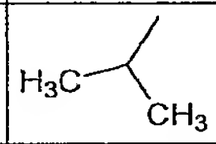
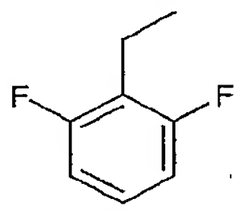
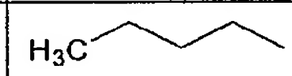
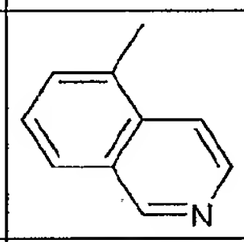
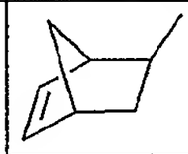
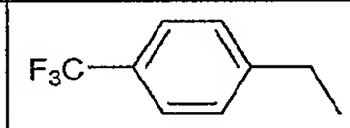
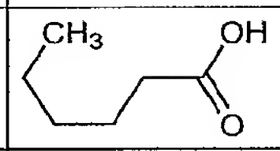
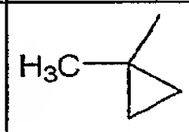
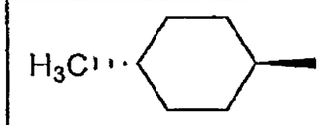
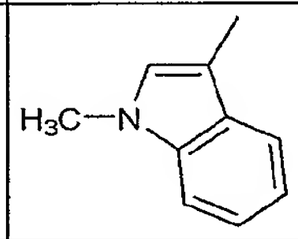
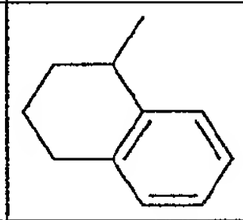
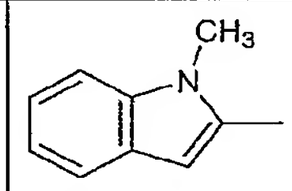
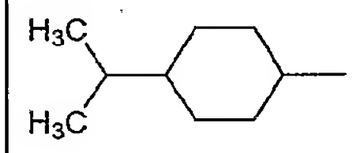
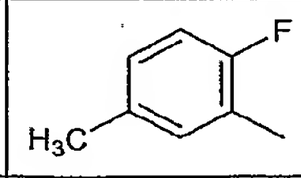
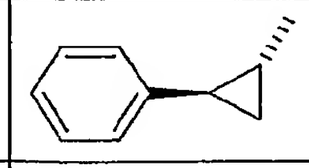
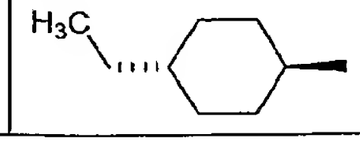
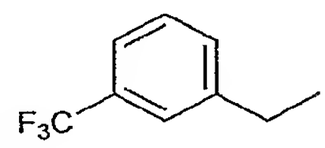
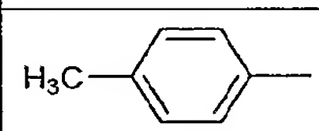
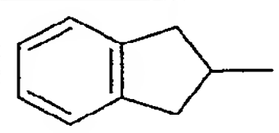
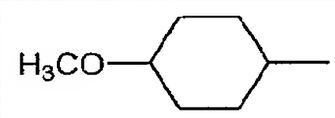
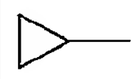
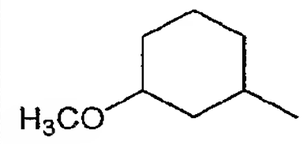
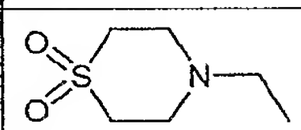
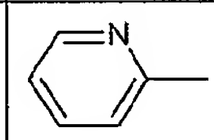
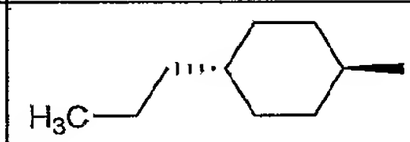
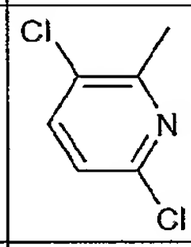
136	
137	
138	
139	
140	
141	
142	
143	
144	
145	
146	
147	
148	
149	
150	
151	

Ex.	B-
152	
153	
154	
155	
156	
157	
158	
159	
160	
161	
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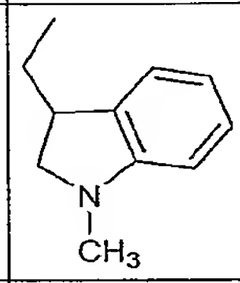
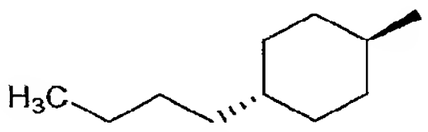
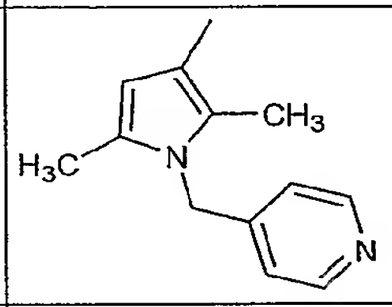
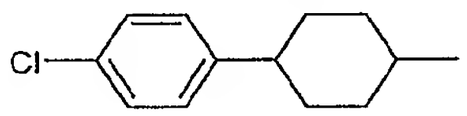
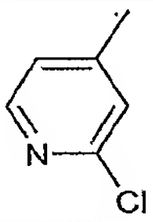
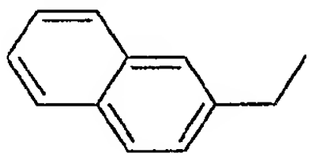
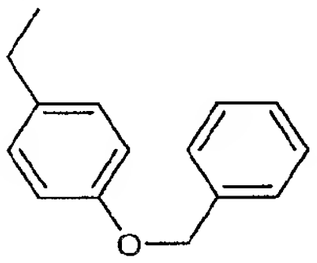
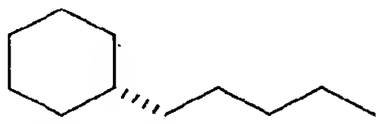
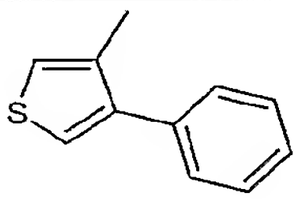
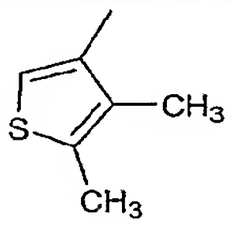
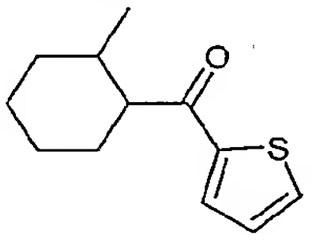
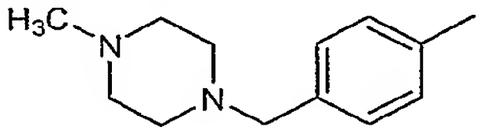
Ex.	B-
168	
169	
170	
171	
172	
173	
174	
175	
177	
178	
179	
180	

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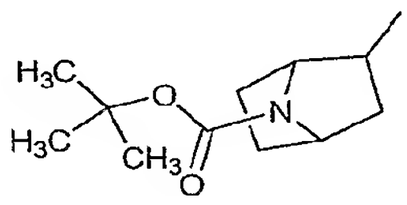
181	
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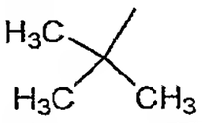
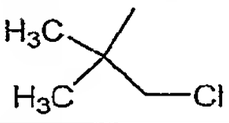
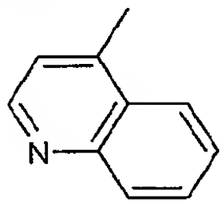
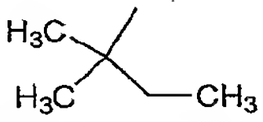
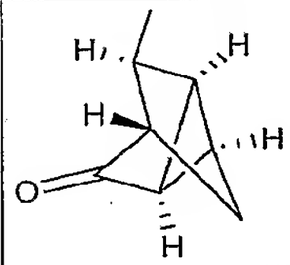
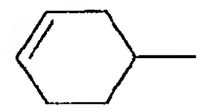
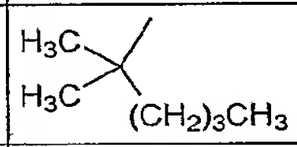
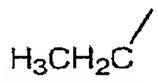
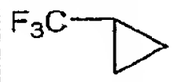
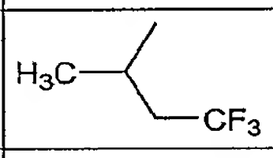
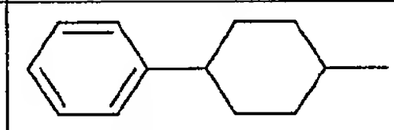
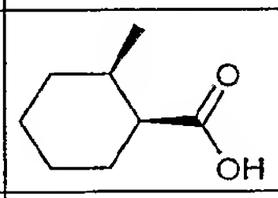
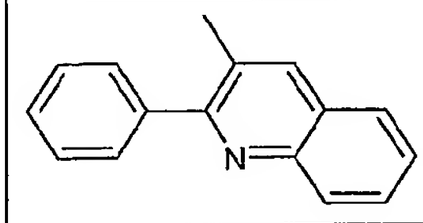
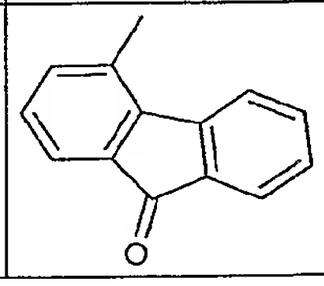
183	
184	
185	
186	
187	
188	
189	
190	
191	
192	
193	
194	
196	
197	

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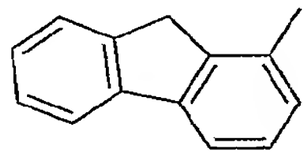
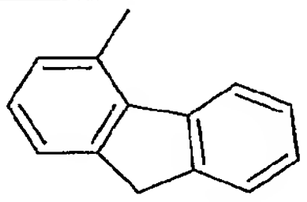
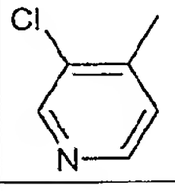
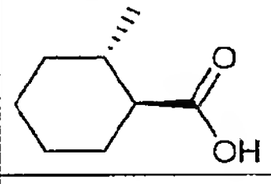
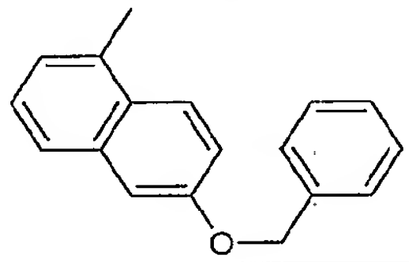
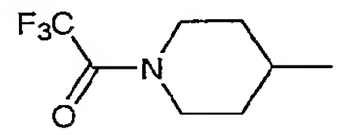
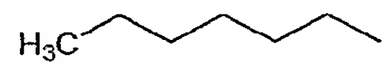
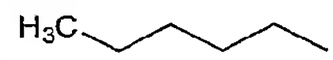
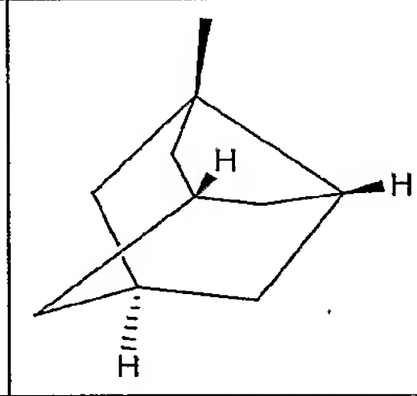
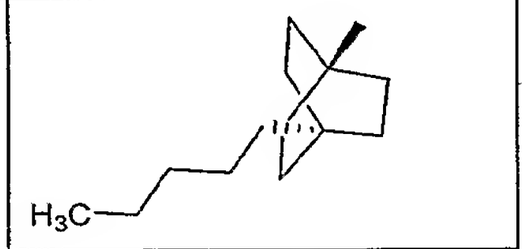
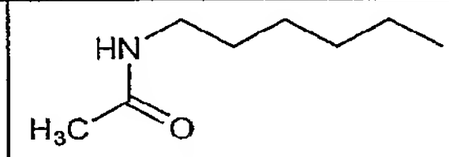
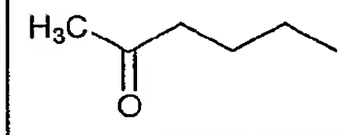
198	
199	
200	
201	
202	
203	
204	
205	
206	
207	
208	
209	
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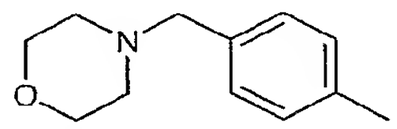
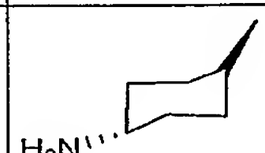
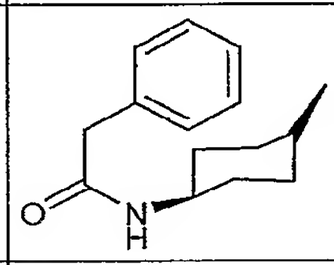
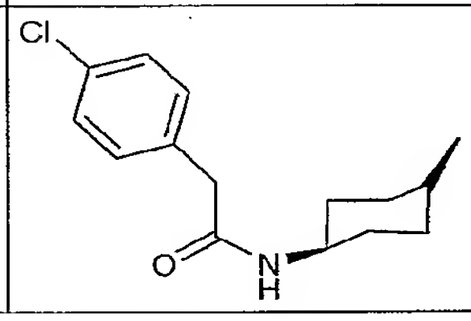
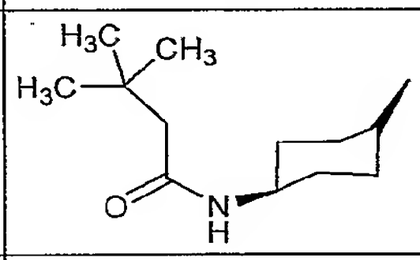
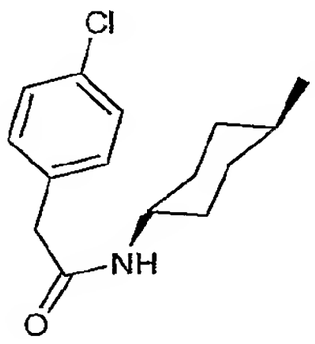
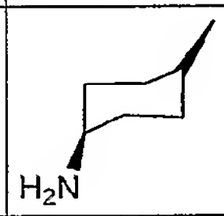
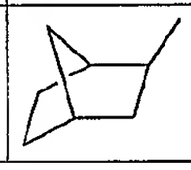
212	
213	
214	
214.1	
214.2	
214.3	
215	
216	

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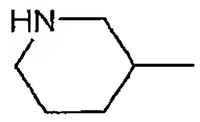
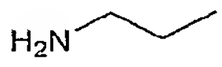
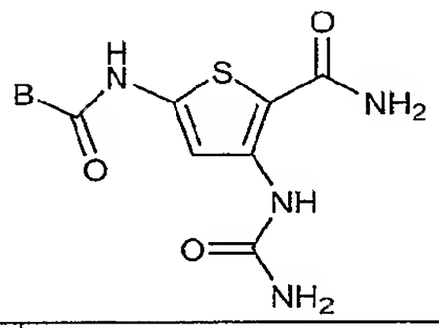
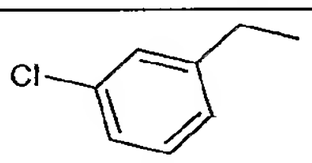
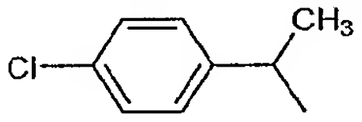
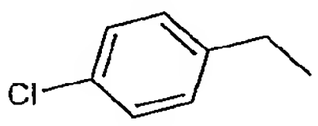
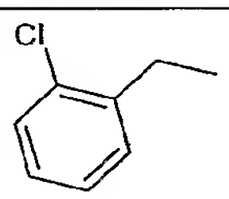
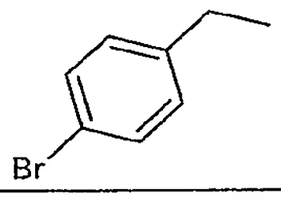
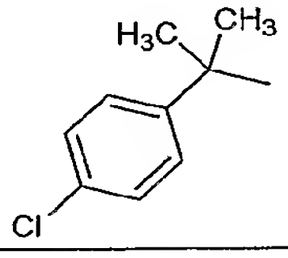
217	
218	

Table II



Ex.	B-
500	
501	
502	
503	
504	
505	

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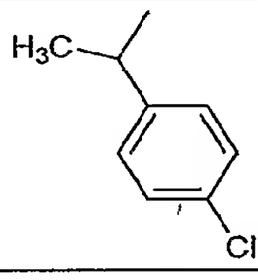
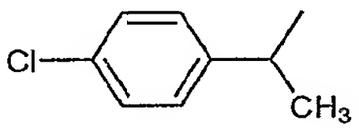
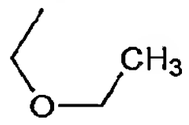
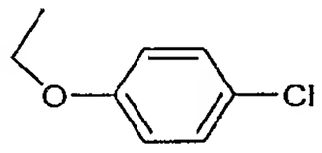
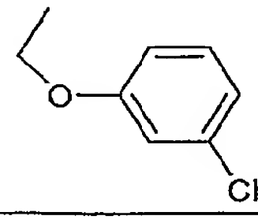
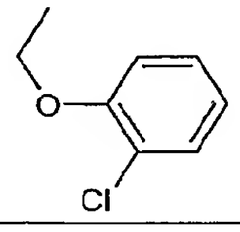
506	
507	
508	
509	
510	
511	

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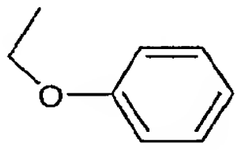
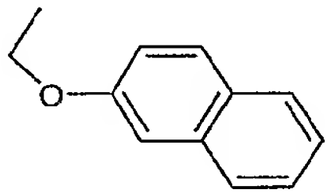
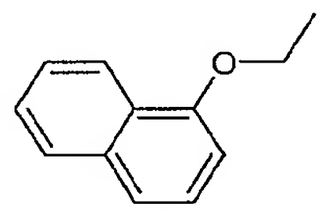
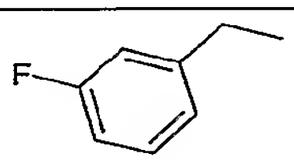
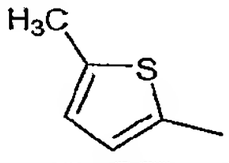
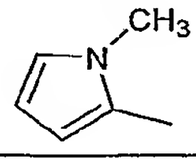
512	
513	
514	
515	
516	
517	

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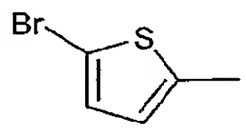
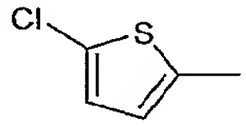
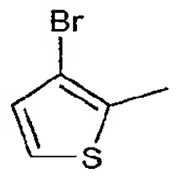
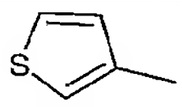
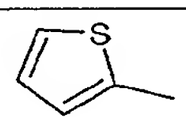
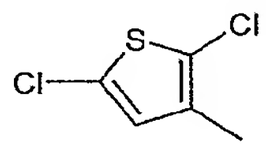
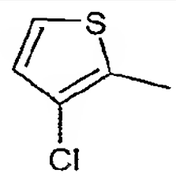
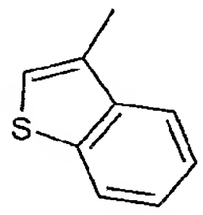
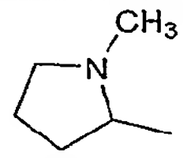
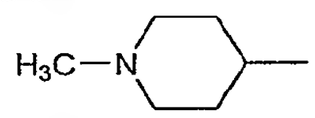
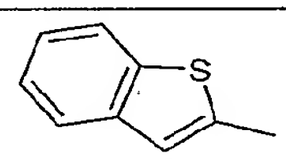
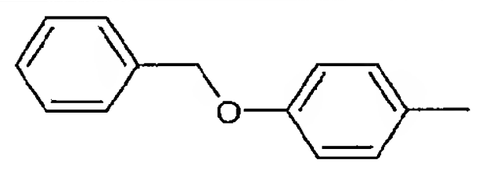
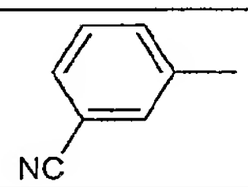
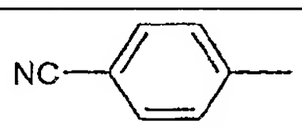
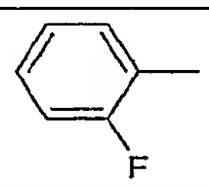
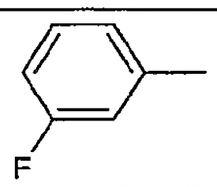
518	
519	
520	
521	
522	
523	
524	
525	
526	
527	
528	
529	
530	
531	
532	
533	

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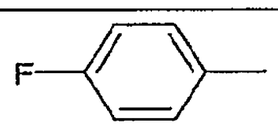
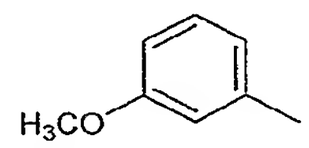
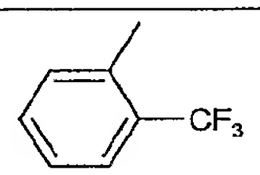
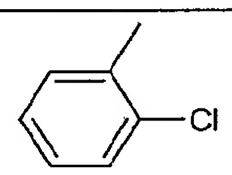
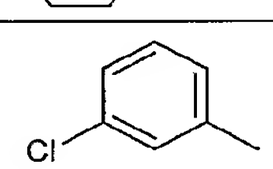
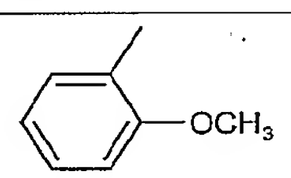
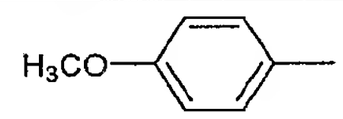
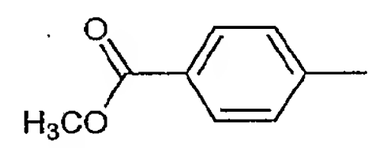
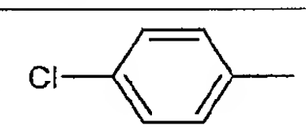
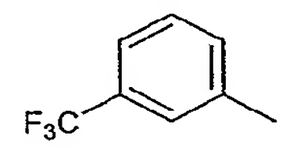
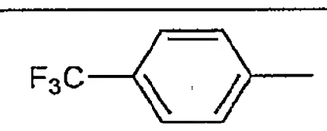
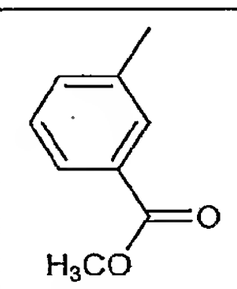
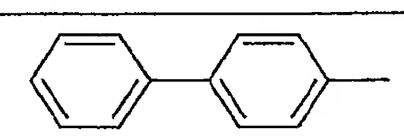
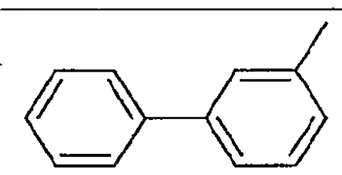
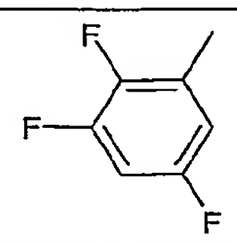
534	
535	
536	
537	
538	
539	
540	
541	
542	
543	
544	
545	
546	
547	
548	

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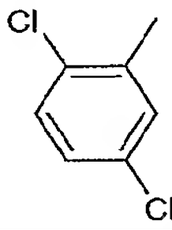
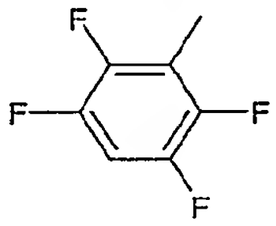
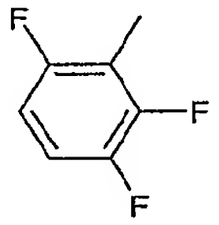
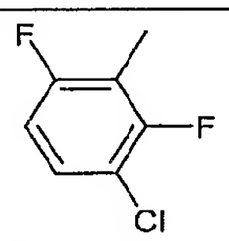
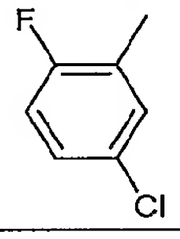
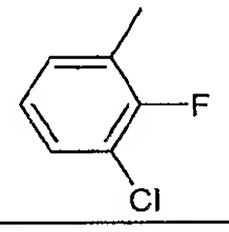
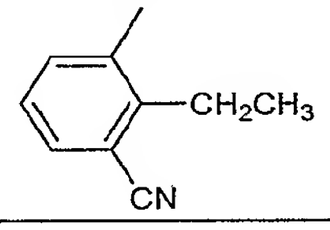
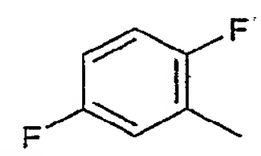
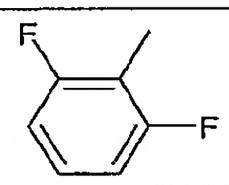
549	
550	
551	
552	
553	
554	
555	
556	
557	
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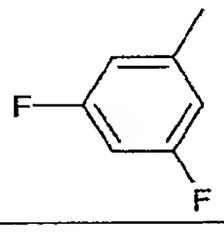
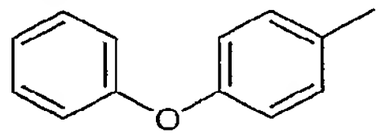
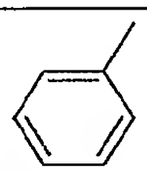
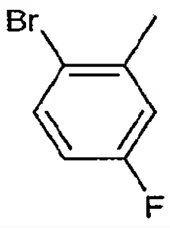
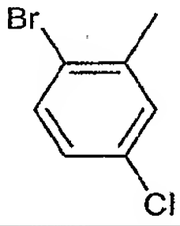
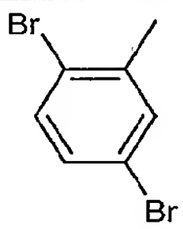
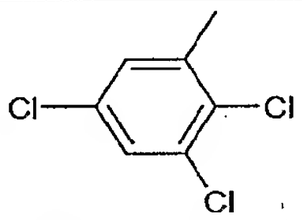
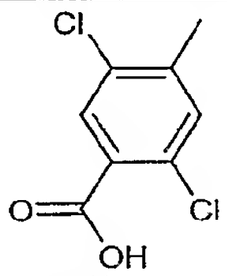
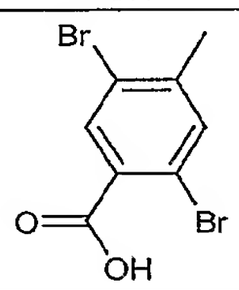
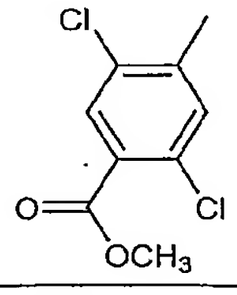
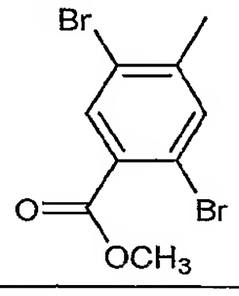
Ex.	B-
561	
562	
563	
564	
565	
566	
567	
568	
569	
570	
571	

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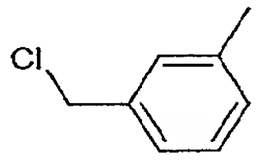
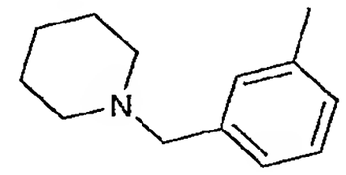
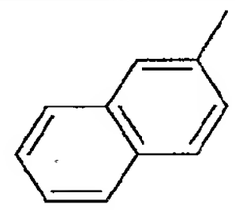
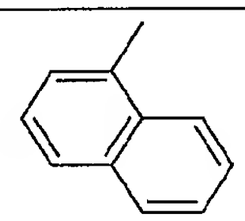
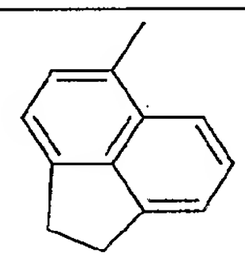
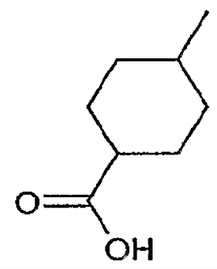
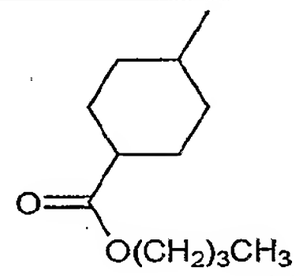
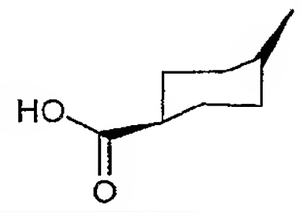
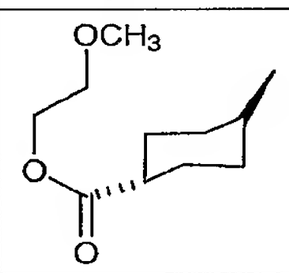
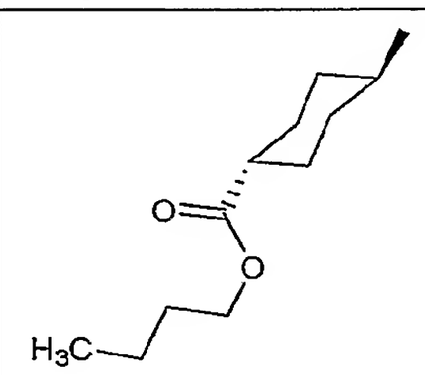
572	
573	
574	
575	
576	
577	
578	
579	
580	
581	

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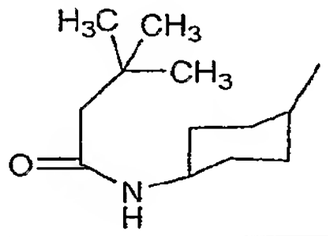
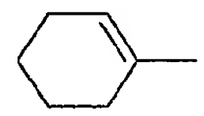
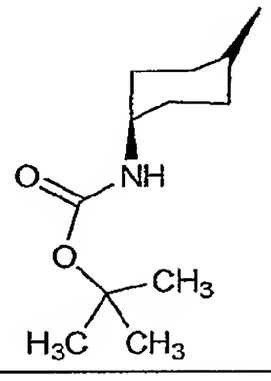
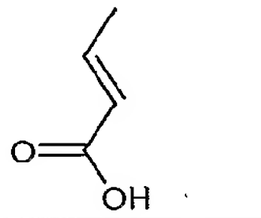
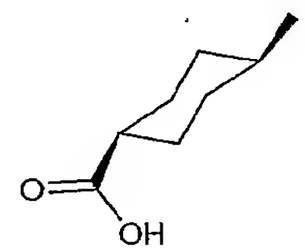
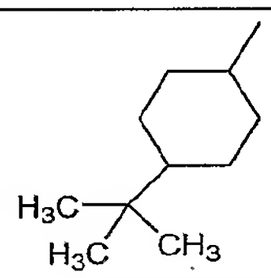
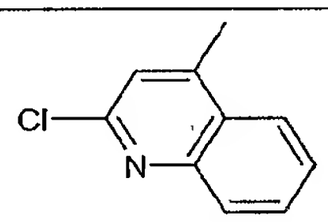
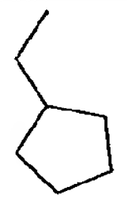
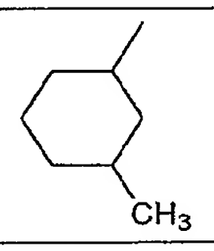
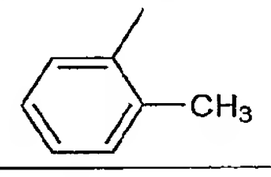
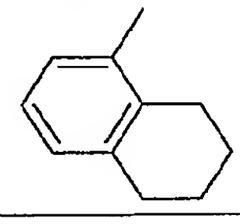
582	
583	
584	
585	
586	
587	
588	
589	
590	
591	
592	

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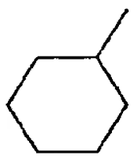
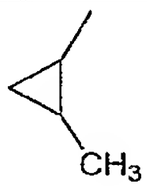
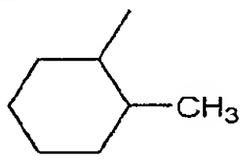
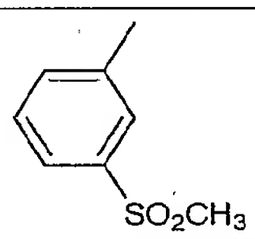
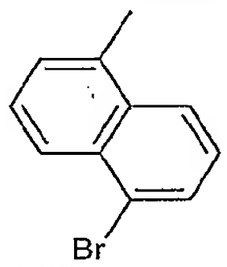
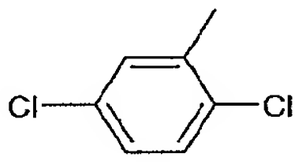
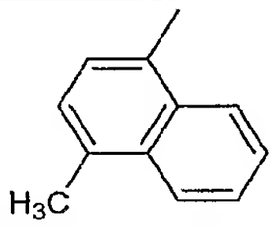
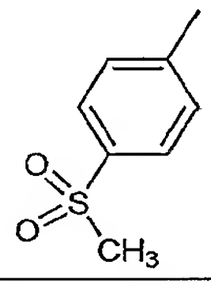
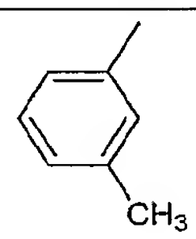
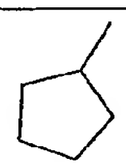
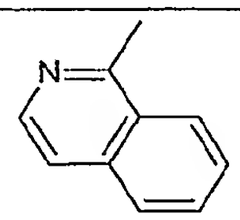
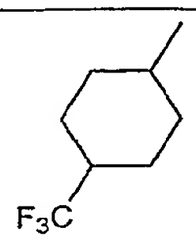
593	
594	
595	
596	
597	
598	
599	
600	
601	
602	
603	
604	

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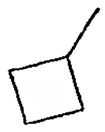
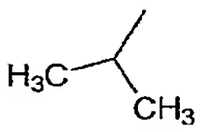
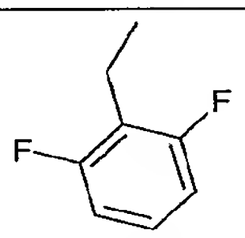
605	
606	
607	
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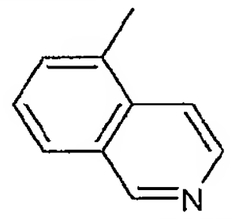
609	
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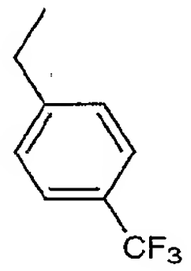
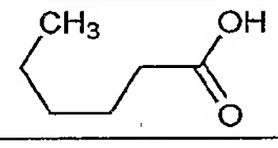
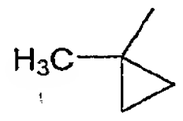
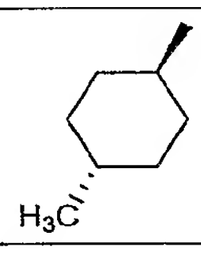
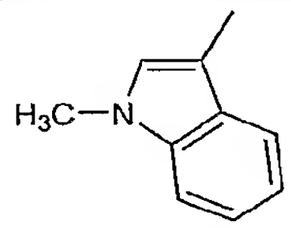
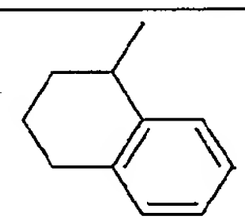
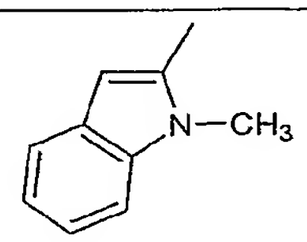
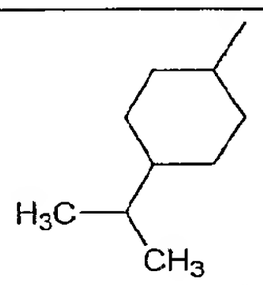
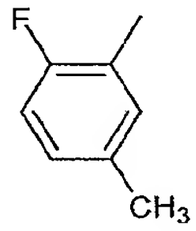
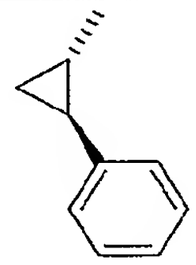
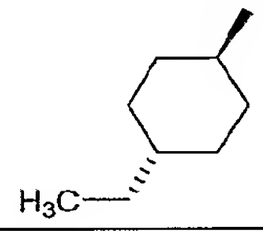
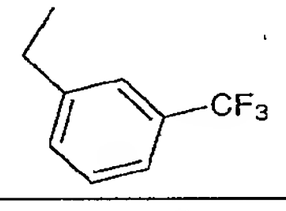
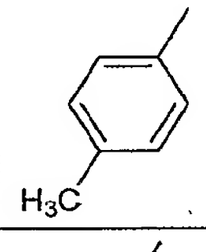
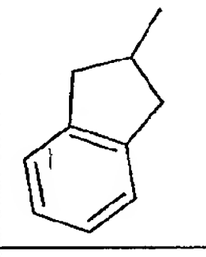
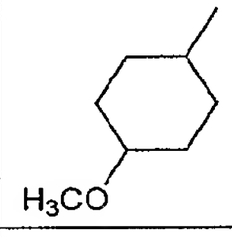
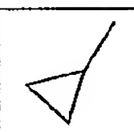
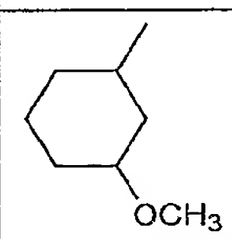
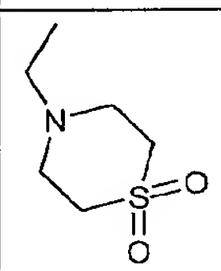
611	
612	
613	
614	
615	
616	
617	

Ex.	B-
618	
619	
620	
621	
622	
623	
624	
625	
626	
627	
628	

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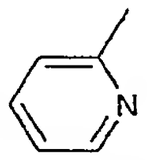
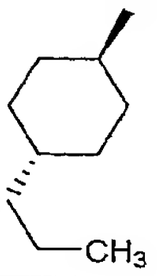
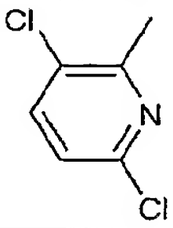
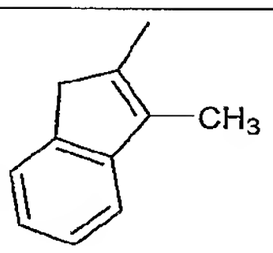
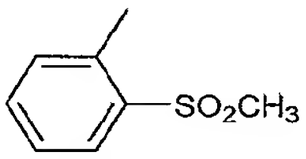
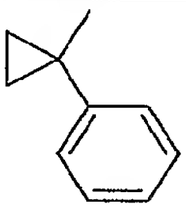
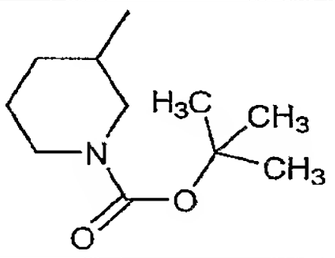
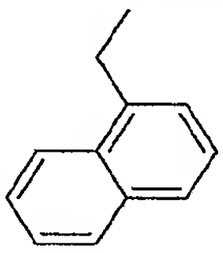
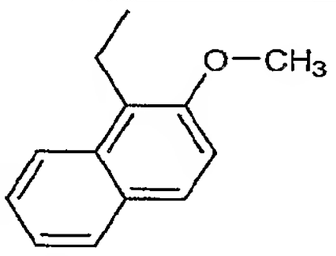
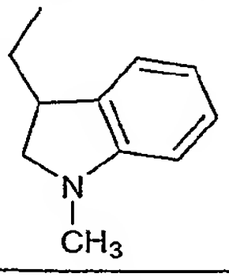
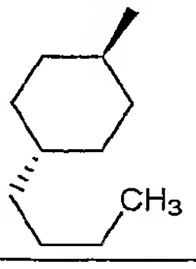
629	
630	
631	
632	
633	
634	
635	
636	
637	
638	
639	

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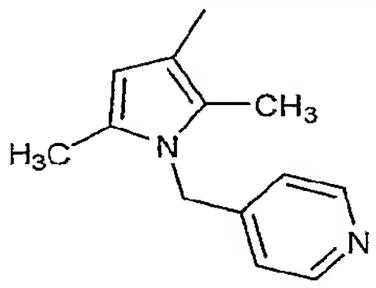
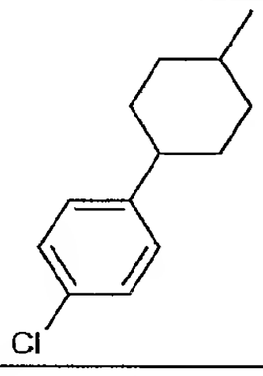
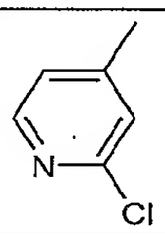
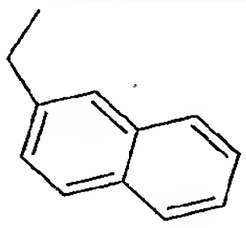
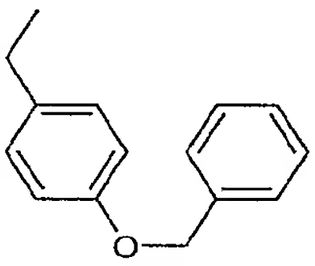
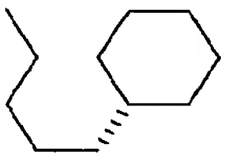
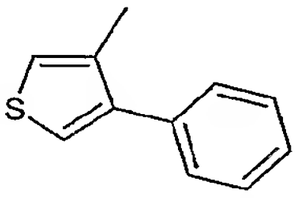
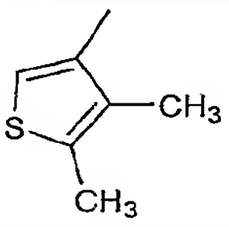
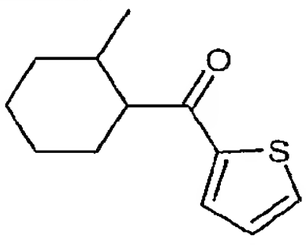
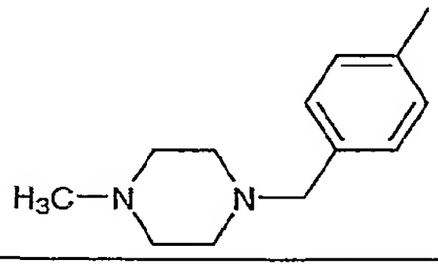
640	
641	
642	
643	
644	
645	
646	
647	
648	
649	

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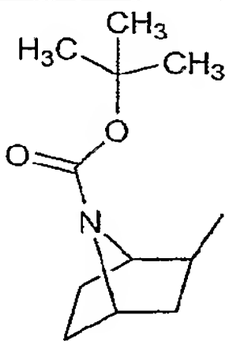
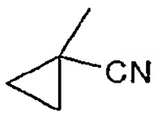
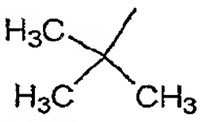
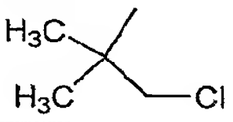
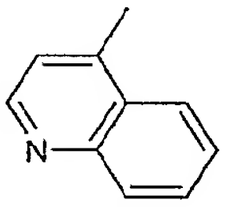
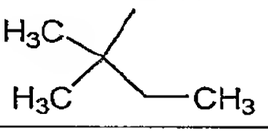
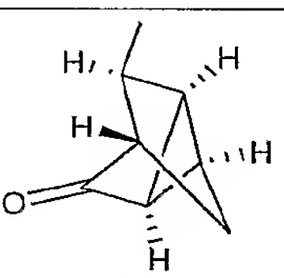
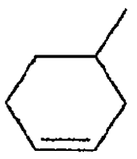
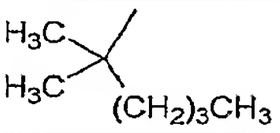
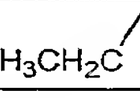
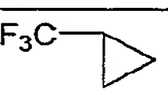
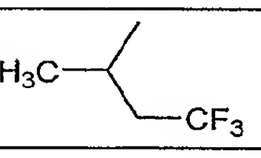
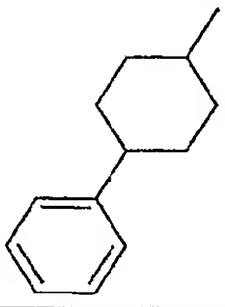
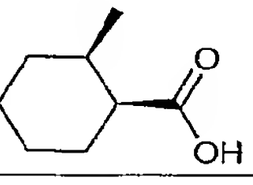
650	
651	
652	
653	
654	
655	
656	
657	
658	
659	
660	
661	
662	
663	

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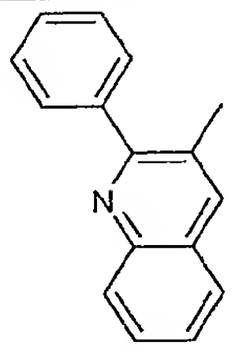
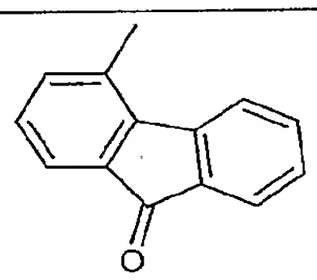
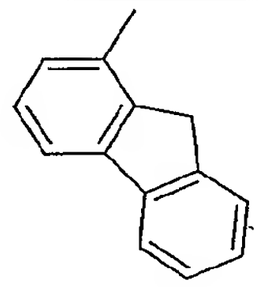
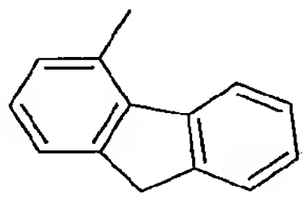
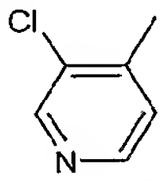
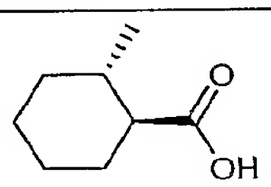
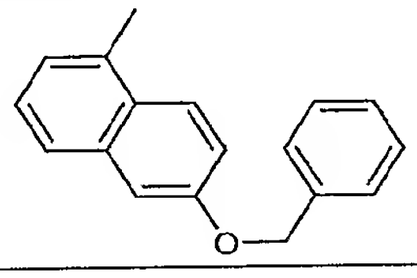
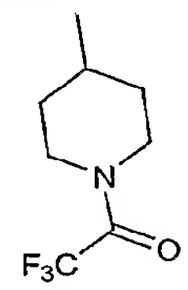
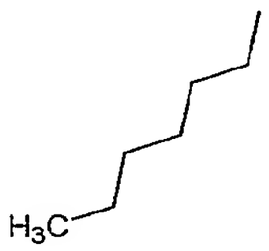
664	
665	
666	
667	
668	
669	
670	
671	
672	

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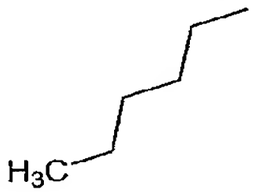
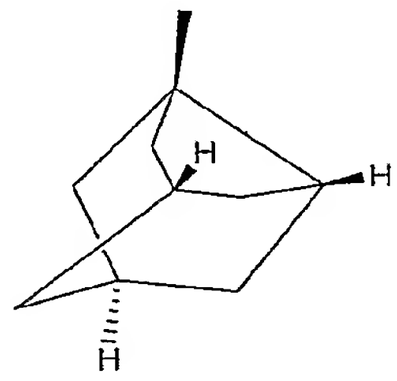
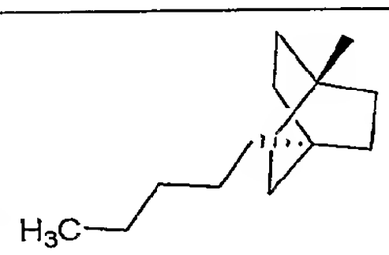
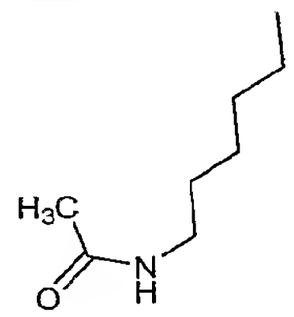
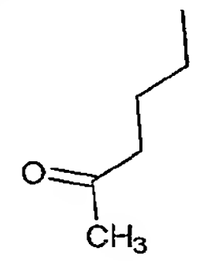
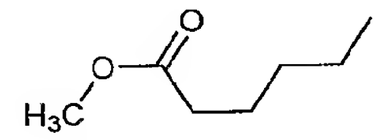
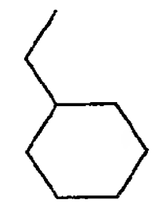
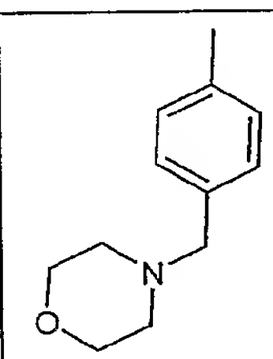
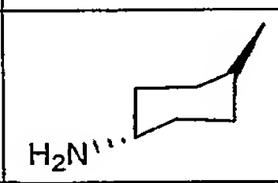
673	
674	
675	
676	
677	
678	
679	
680	
681	

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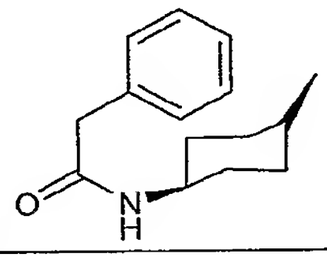
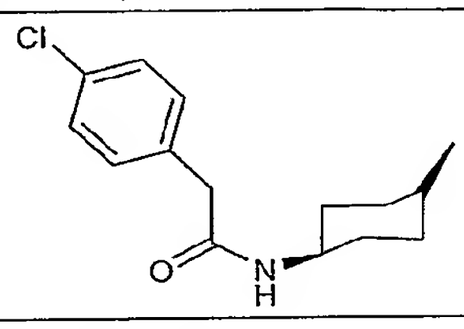
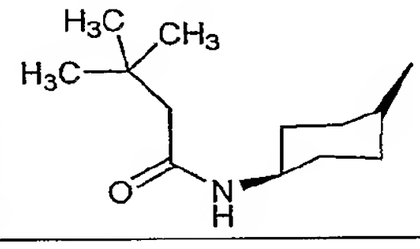
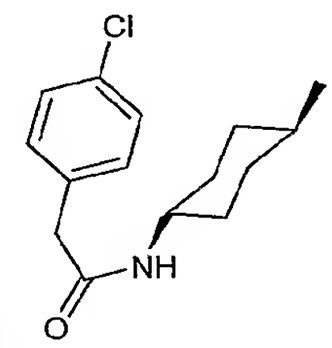
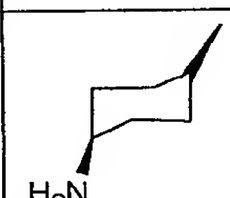
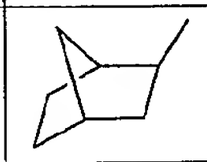
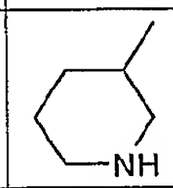
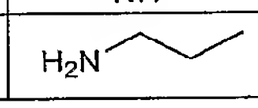
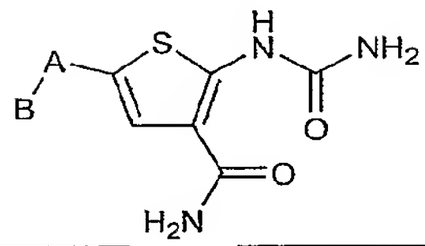
682	
683	
684	
685	
686	
687	
688	
689	

Table III



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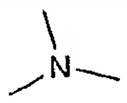
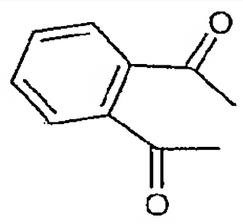
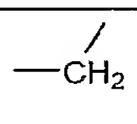
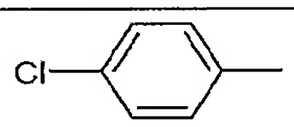
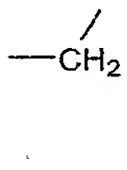
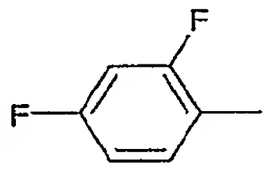
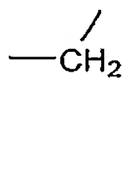
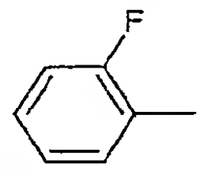
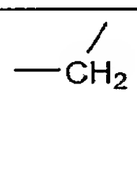
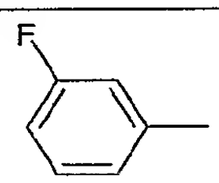
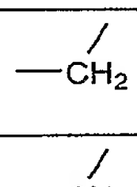
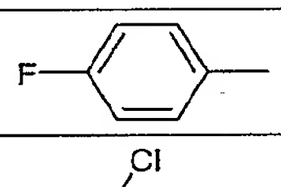
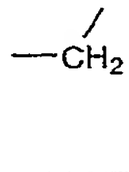
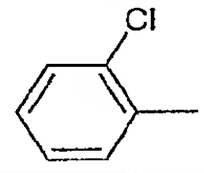
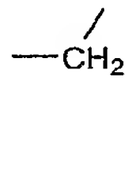
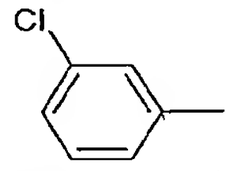
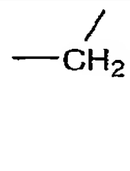
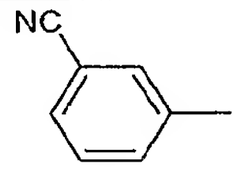
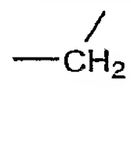
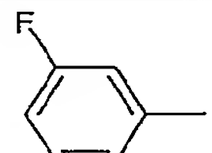
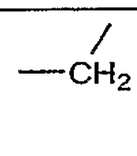
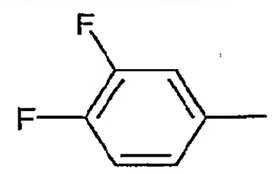
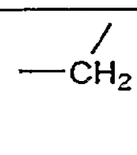
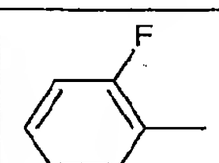
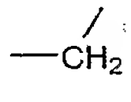
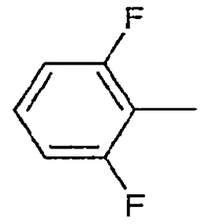
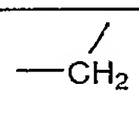
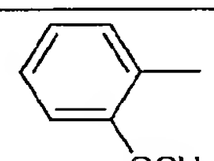
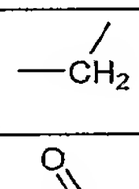
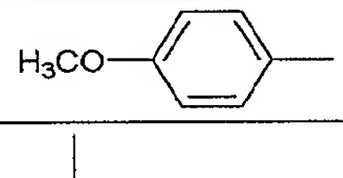
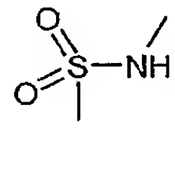
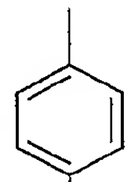
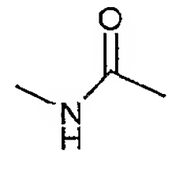
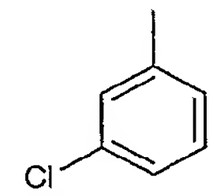
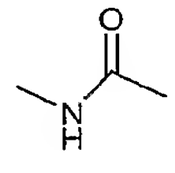
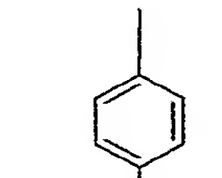
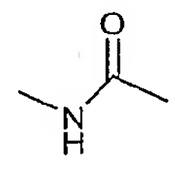
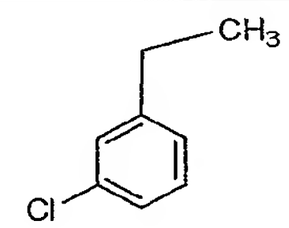
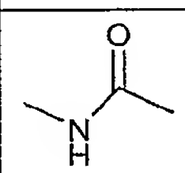
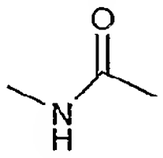
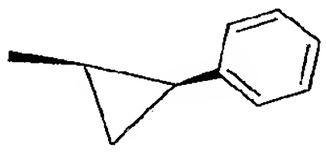
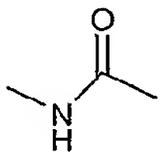
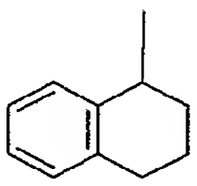
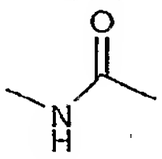
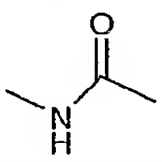
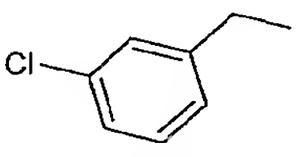
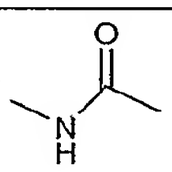
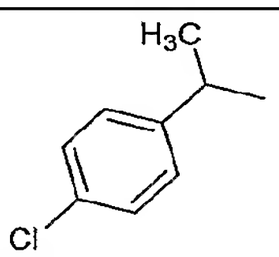
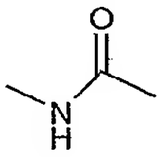
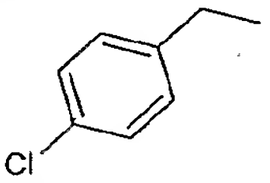
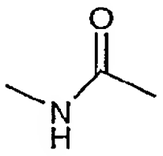
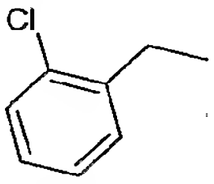
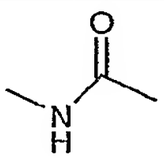
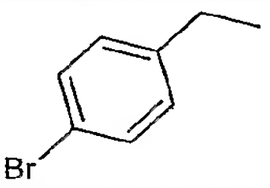
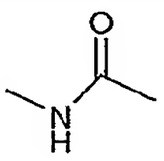
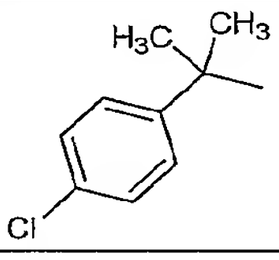
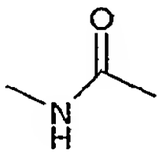
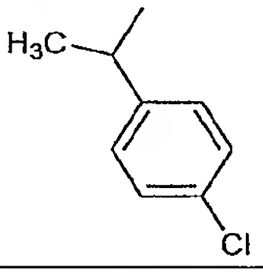
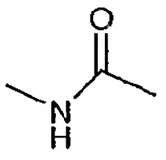
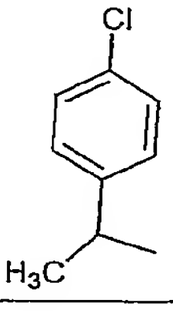
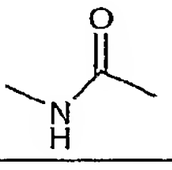
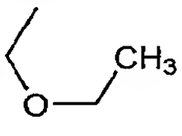
31A, 31B		
80		
81		
84		
85		
86		
87		
88		
89		
90		
91		
96		

Ex.	-A-	B-
97		
99		
100		
122		
303		
304		
305		
306		
307		
308		

Ex.	-A-	B-
309		
310		
312		—H
690		
691		
692		
693		
694		
695		
696		
697		
698		

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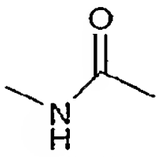
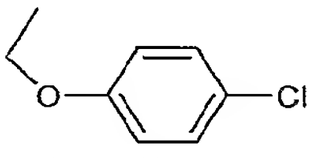
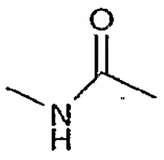
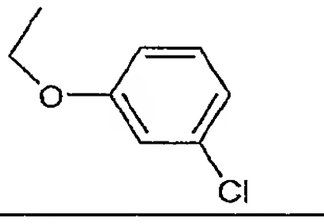
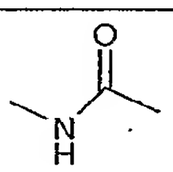
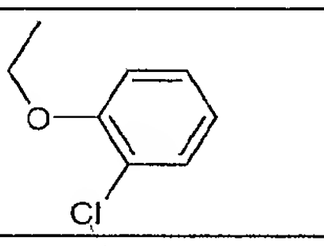
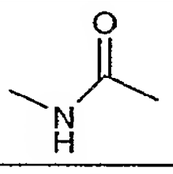
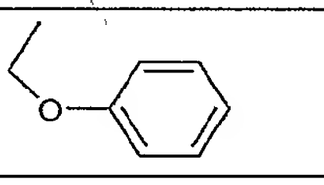
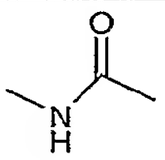
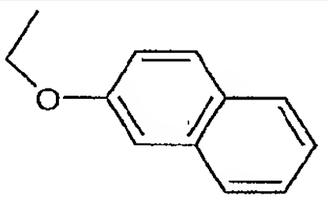
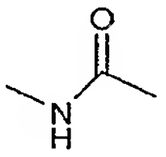
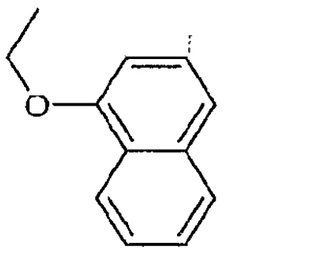
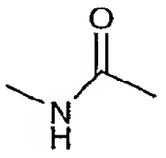
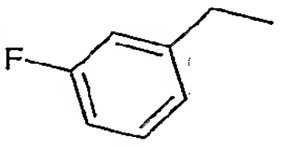
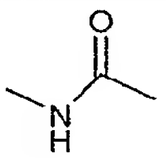
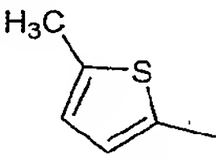
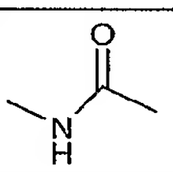
699		
700		
701		
702		
703		
704		
705		
706		
707		
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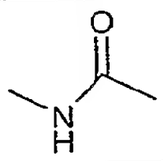
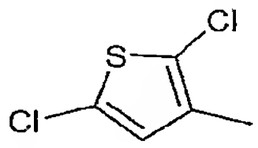
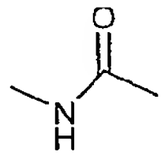
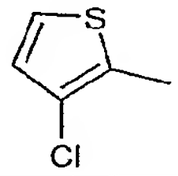
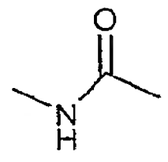
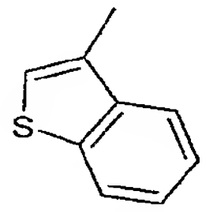
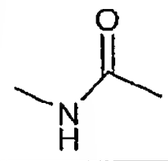
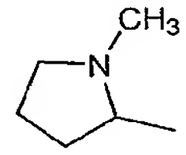
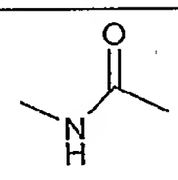
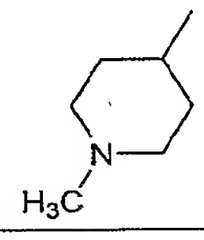
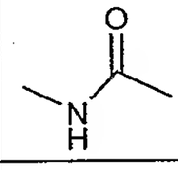
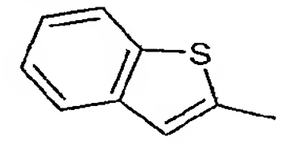
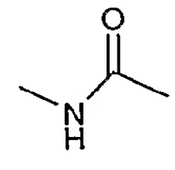
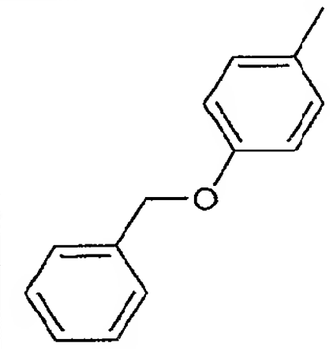
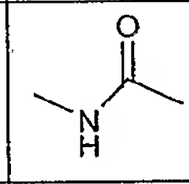
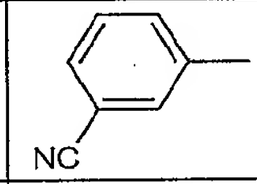
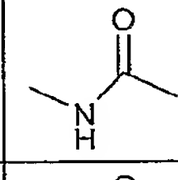
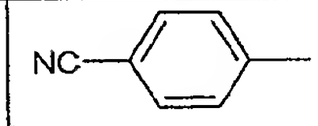
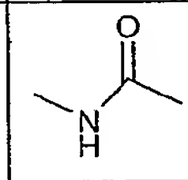
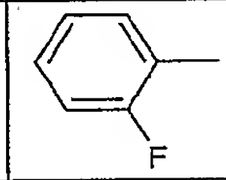
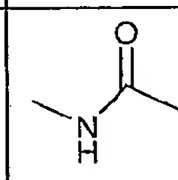
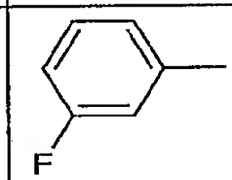
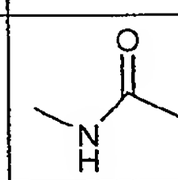
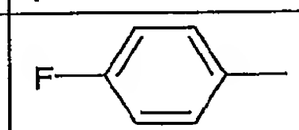
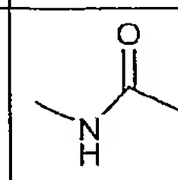
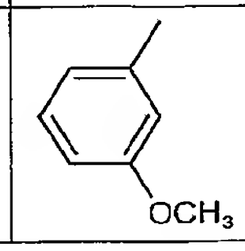
713		
714		
715		
716		
717		
718		
719		
720		
721		
722		
723		
724		
725		

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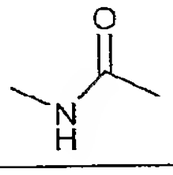
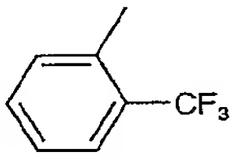
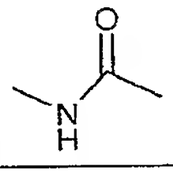
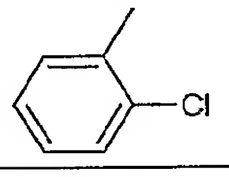
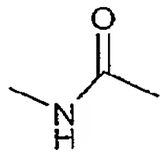
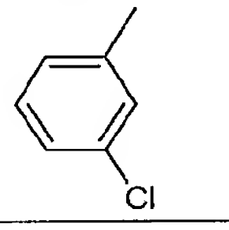
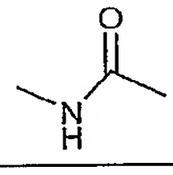
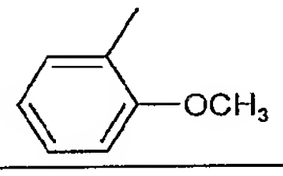
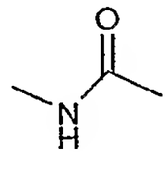
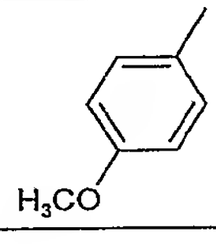
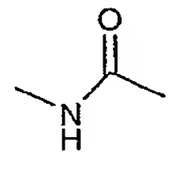
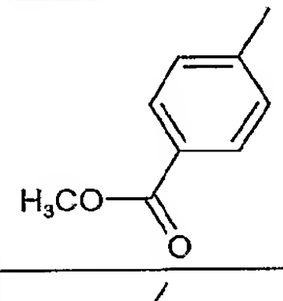
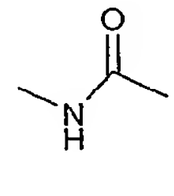
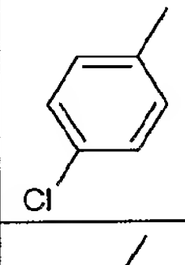
726		
727		
728		
729		
730		
731		
732		
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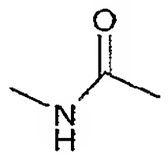
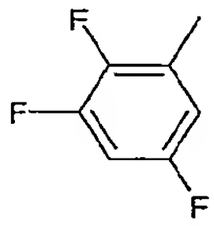
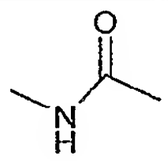
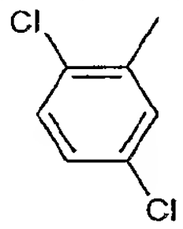
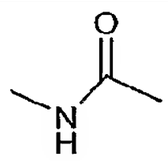
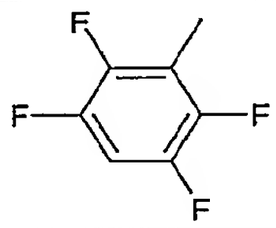
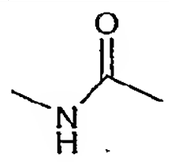
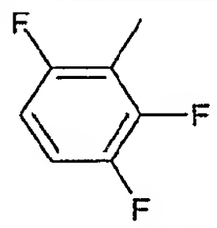
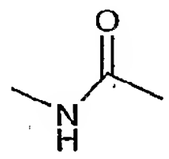
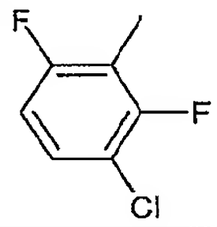
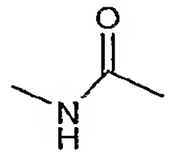
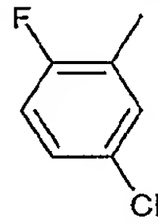
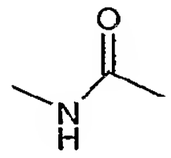
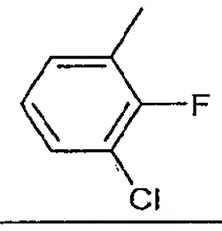
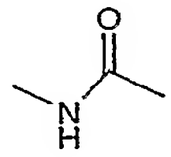
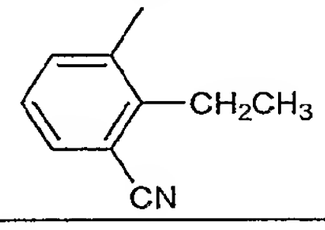
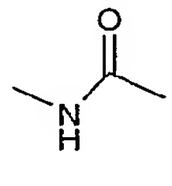
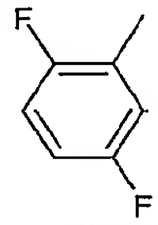
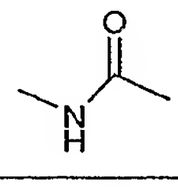
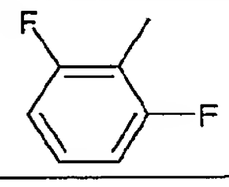
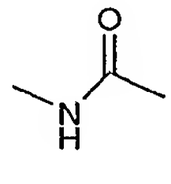
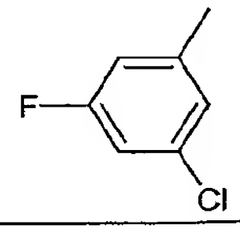
738		
739		
740		
741		
742		
743		
744		
745		
746		
747		
748		

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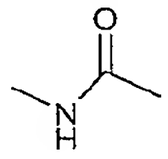
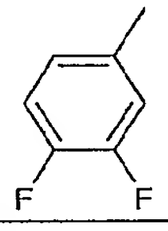
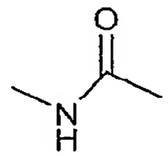
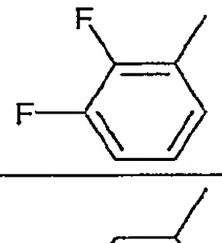
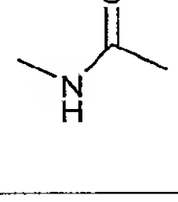
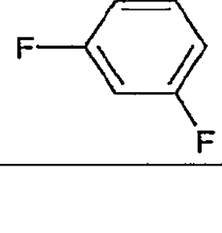
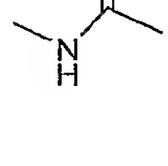
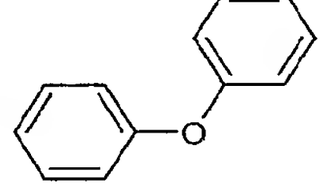
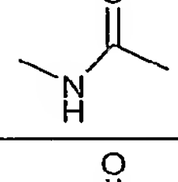
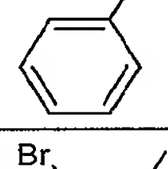
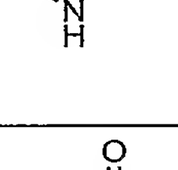
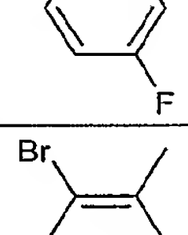
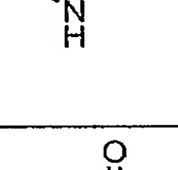
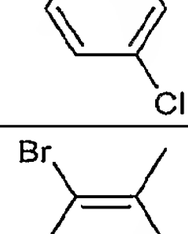
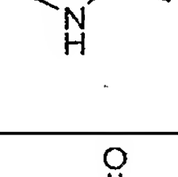
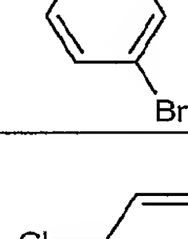
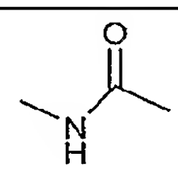
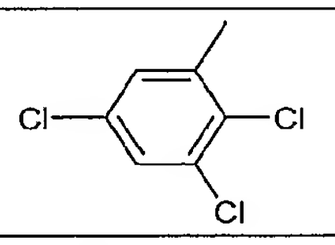
749		
750		
751		
752		
753		
754		
755		
756		
757		
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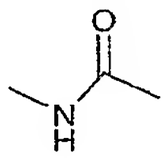
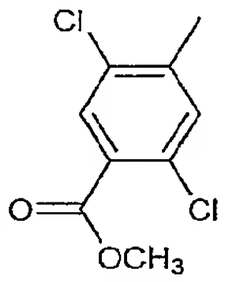
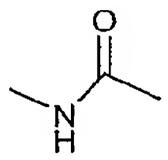
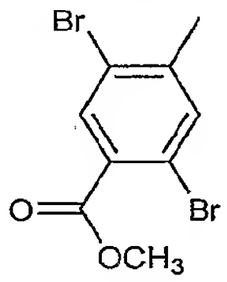
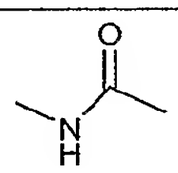
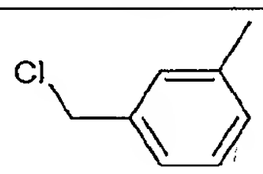
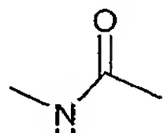
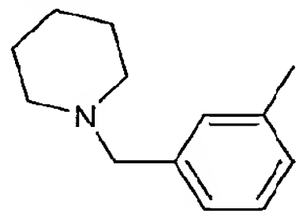
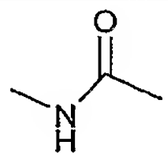
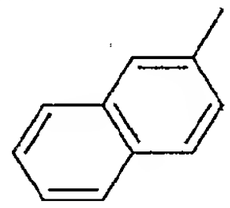
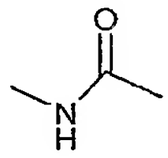
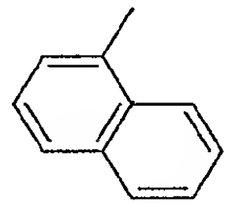
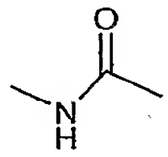
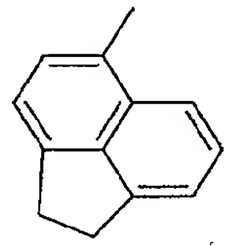
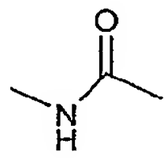
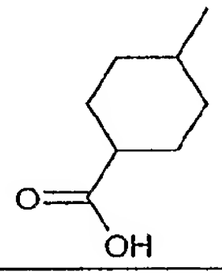
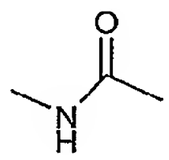
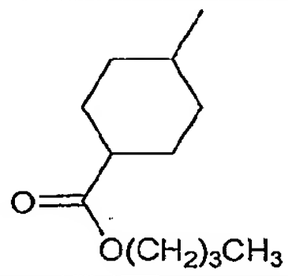
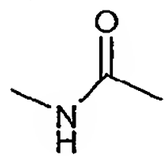
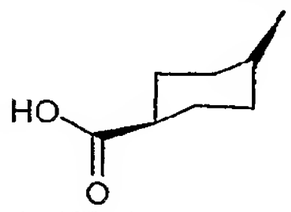
760		
761		
762		
763		
764		
765		
766		
767		
768		
769		

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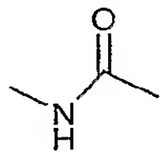
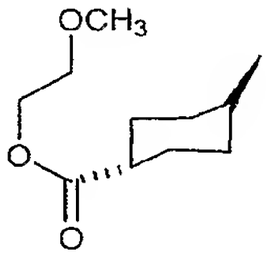
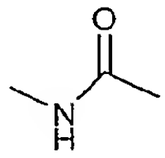
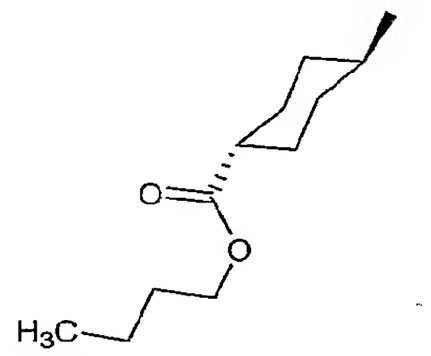
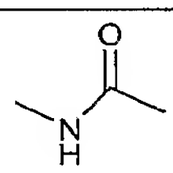
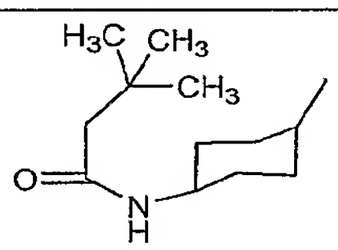
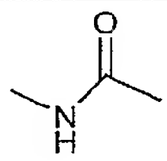
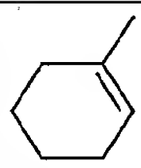
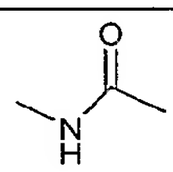
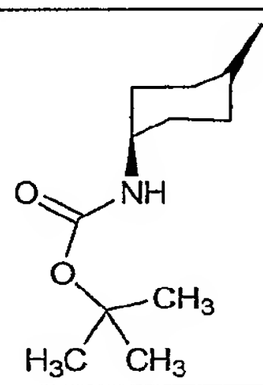
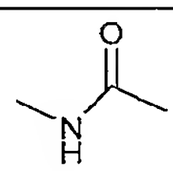
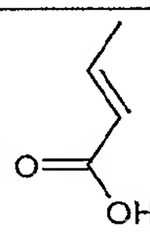
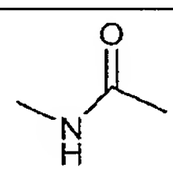
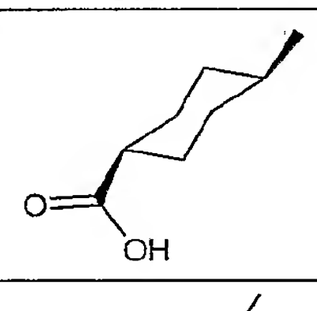
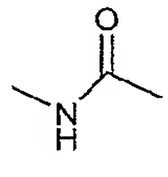
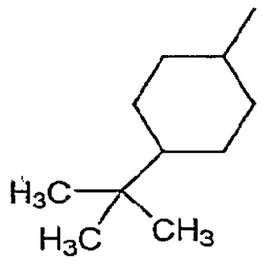
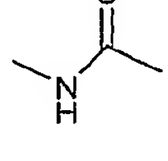
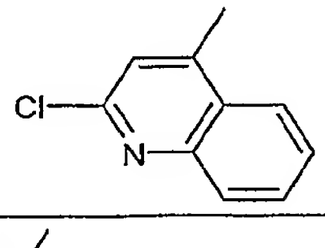
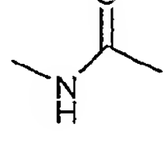
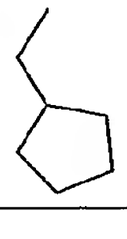
770		
771		
772		
773		
774		
775		
776		
777		
778		
779		

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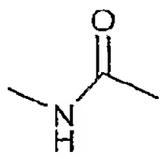
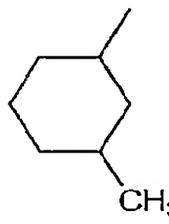
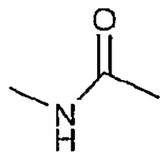
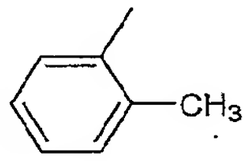
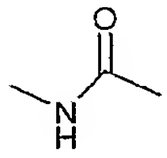
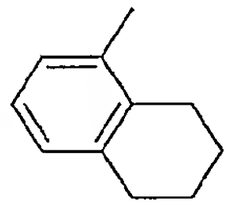
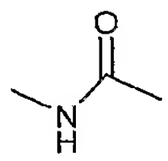
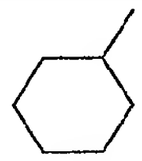
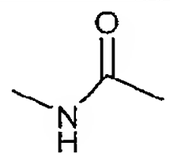
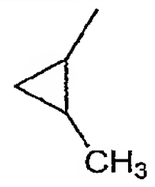
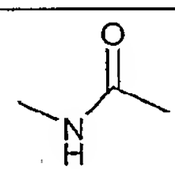
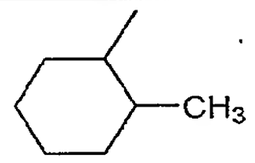
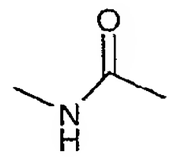
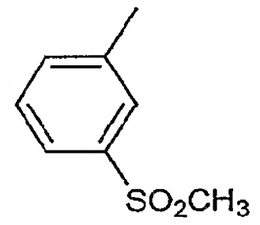
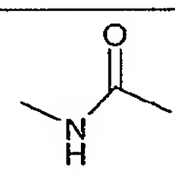
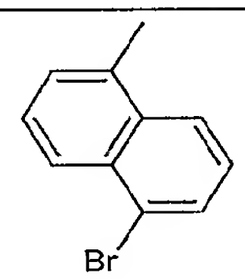
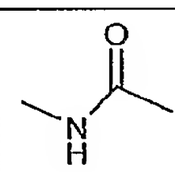
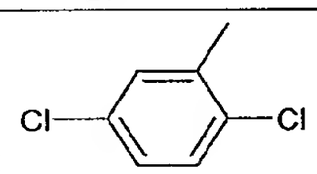
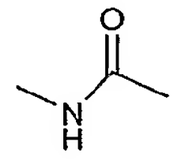
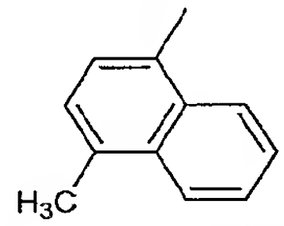
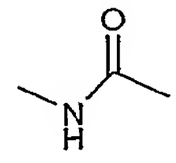
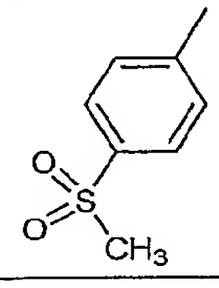
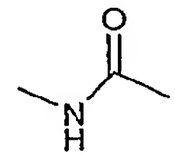
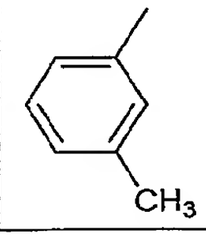
780		
781		
782		
783		
784		
785		
786		
787		
788		
789		
790		
791		

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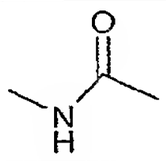
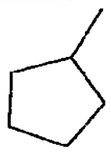
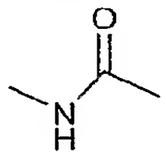
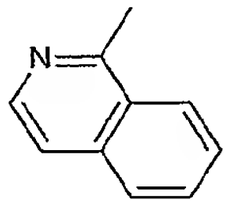
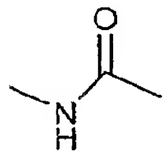
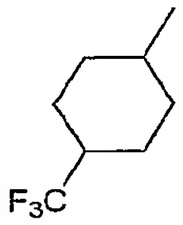
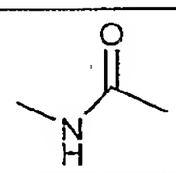
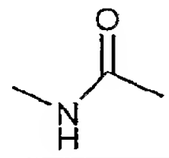
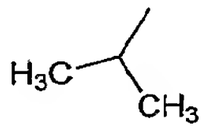
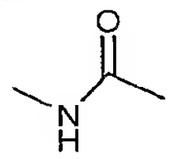
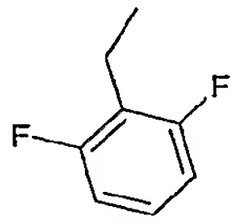
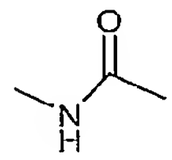
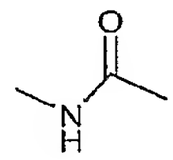
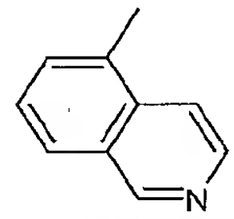
792		
793		
794		
795		
796		
797		
798		
799		
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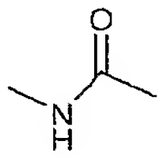
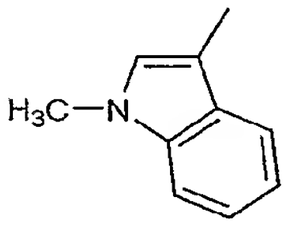
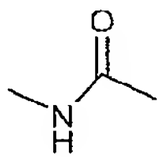
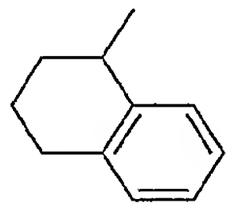
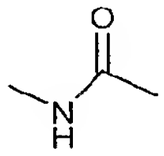
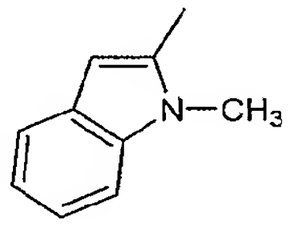
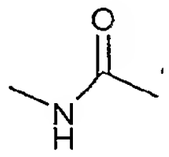
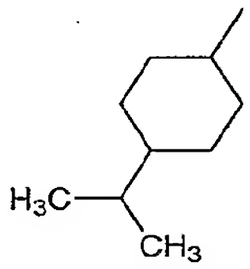
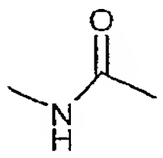
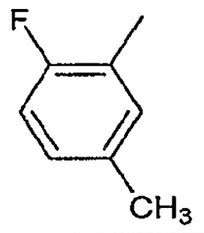
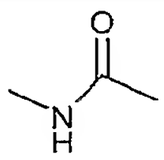
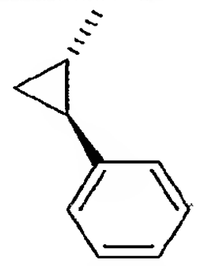
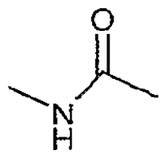
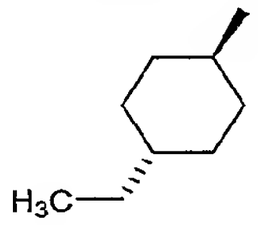
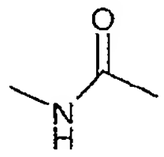
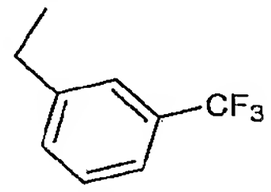
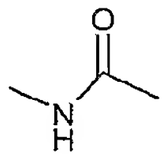
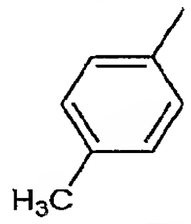
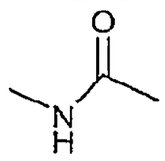
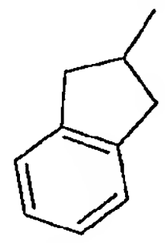
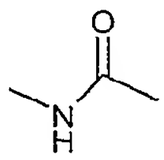
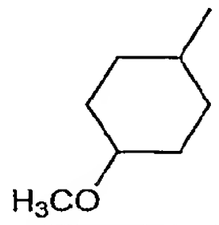
805		
806		
807		
808		
809		
810		
811		
812		
813		
814		
815		

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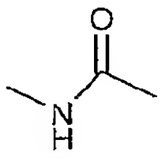
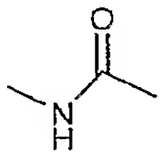
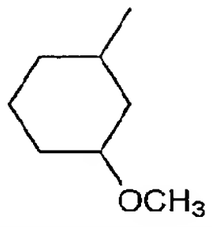
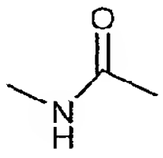
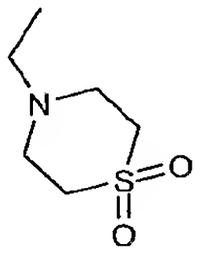
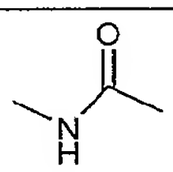
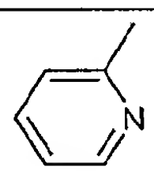
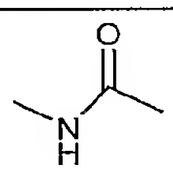
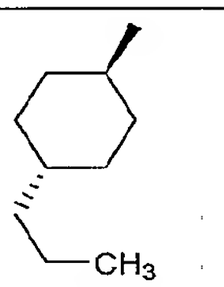
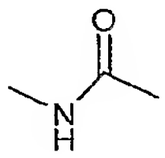
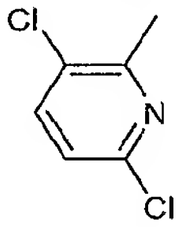
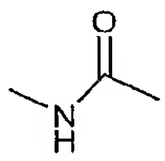
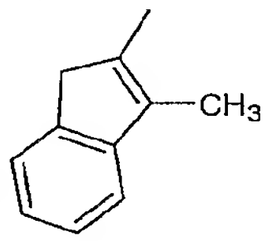
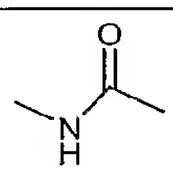
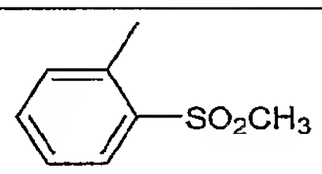
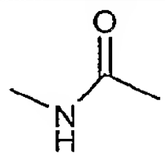
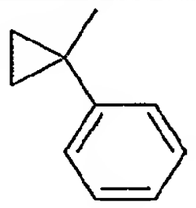
816		
817		
818		
819		
820		
821		
822		
823		
824		
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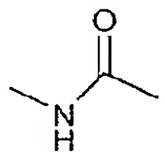
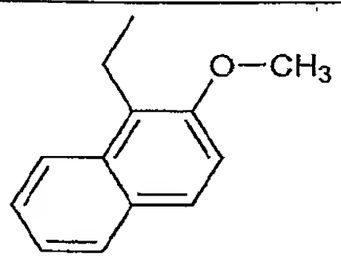
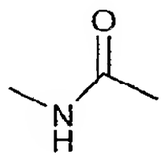
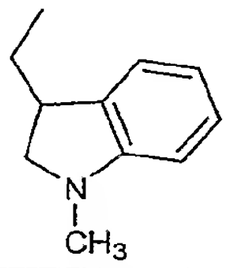
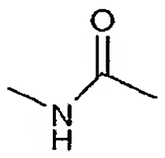
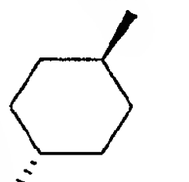
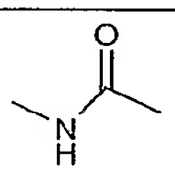
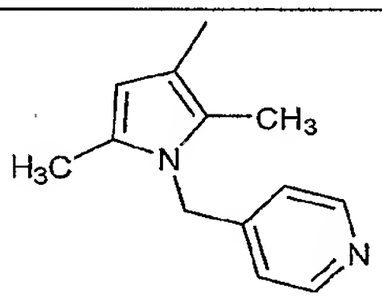
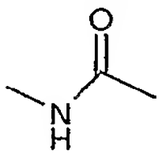
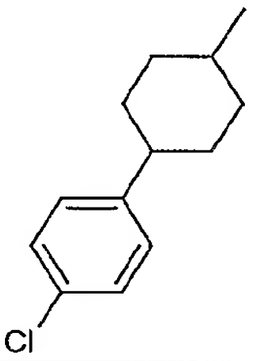
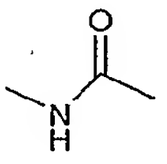
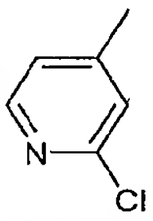
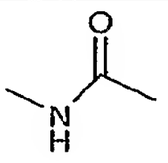
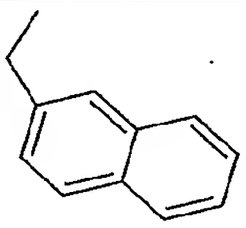
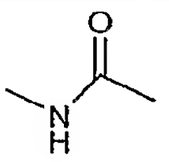
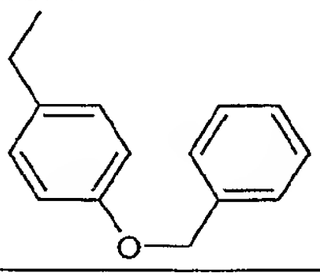
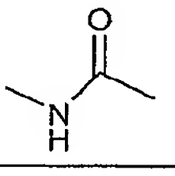
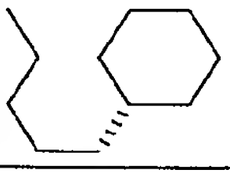
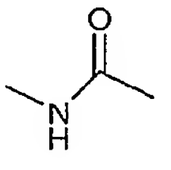
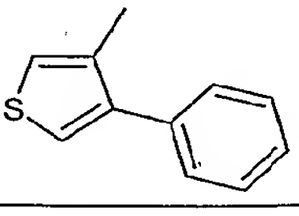
827		
828		
829		
830		
831		
832		
833		
834		
835		
836		

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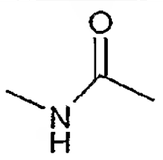
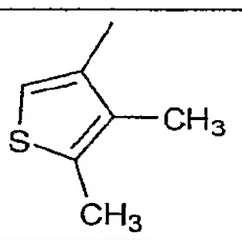
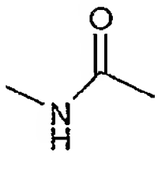
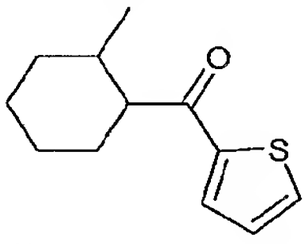
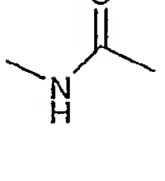
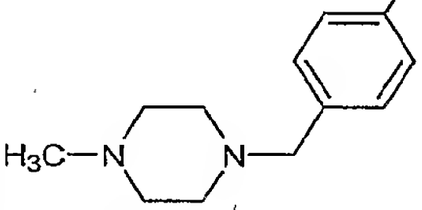
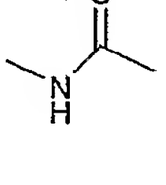
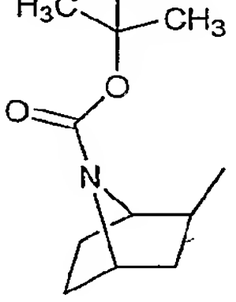
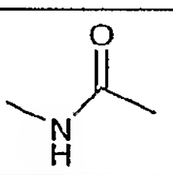
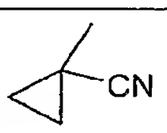
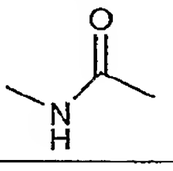
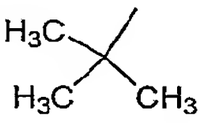
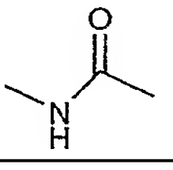
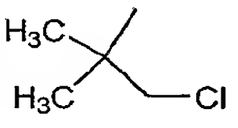
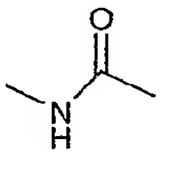
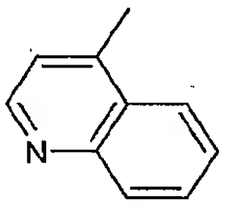
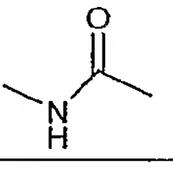
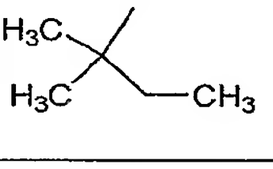
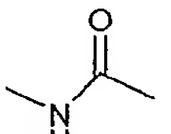
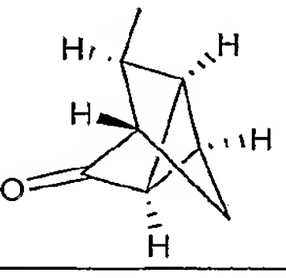
837		
838		
839		
840		
841		
842		
843		
844		
845		
846		
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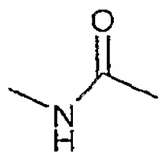
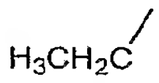
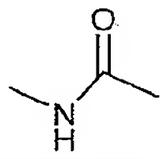
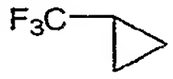
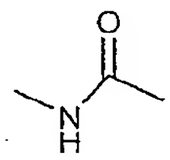
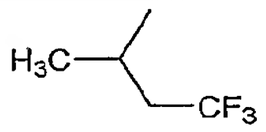
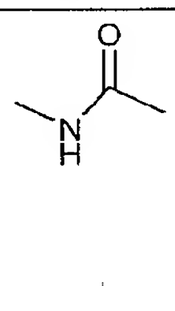
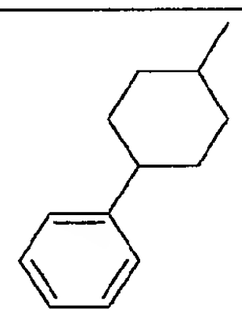
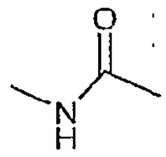
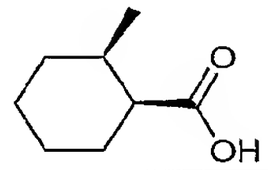
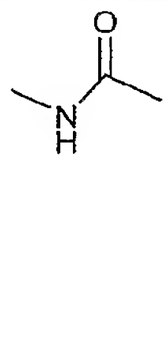
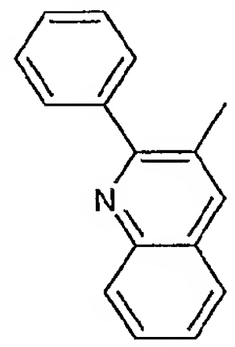
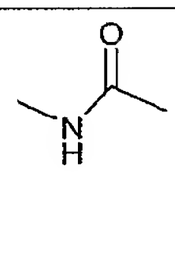
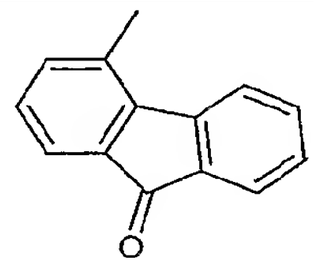
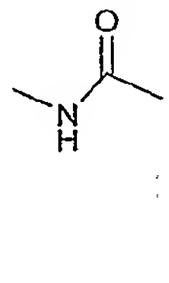
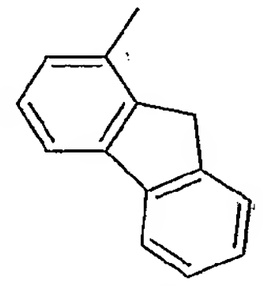
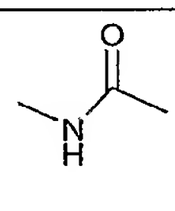
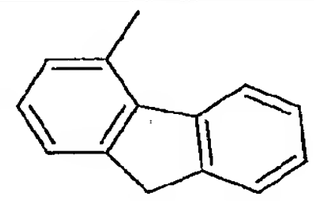
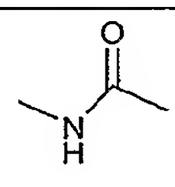
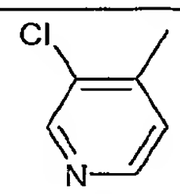
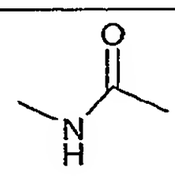
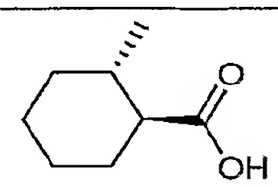
849		
850		
851		
852		
853		
854		
855		
856		
857		
858		
859		

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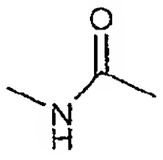
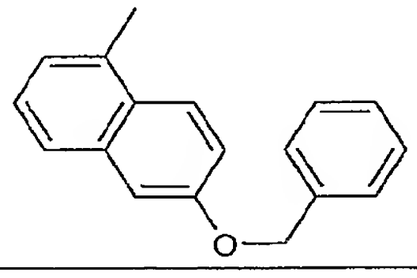
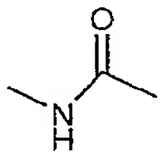
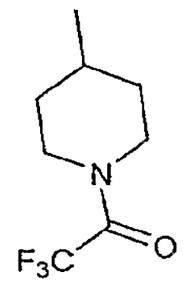
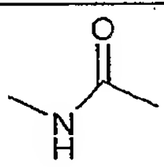
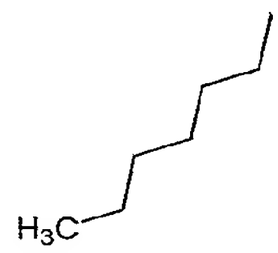
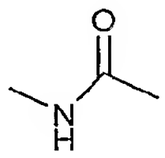
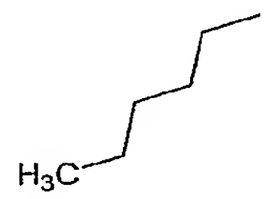
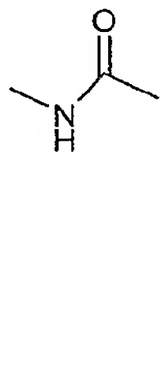
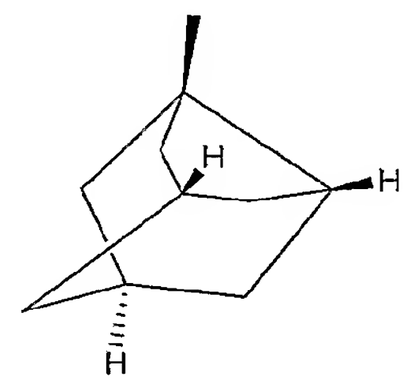
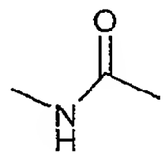
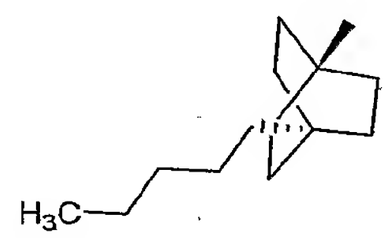
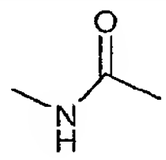
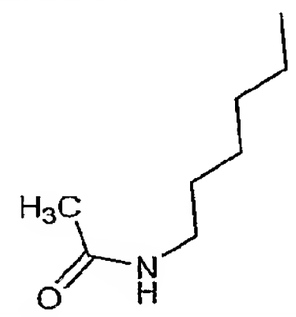
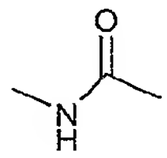
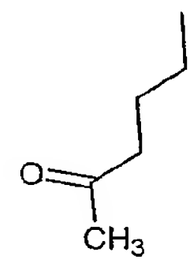
860		
861		
862		
863		
864		
865		
866		
867		

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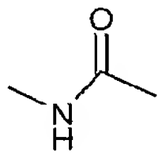
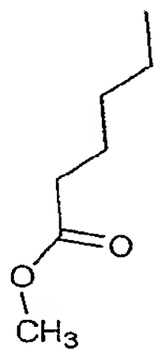
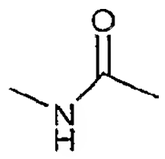
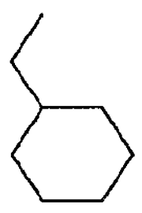
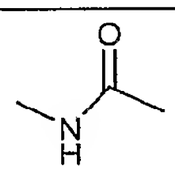
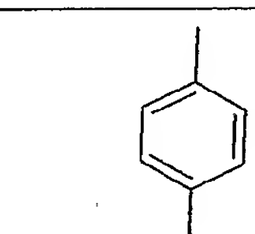
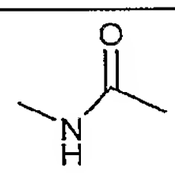
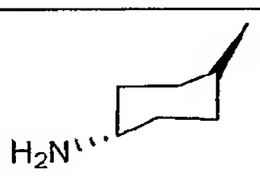
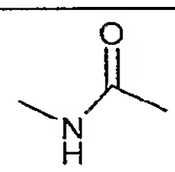
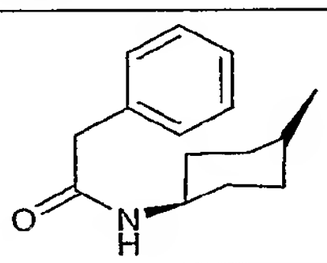
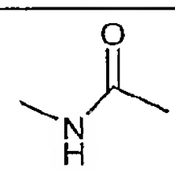
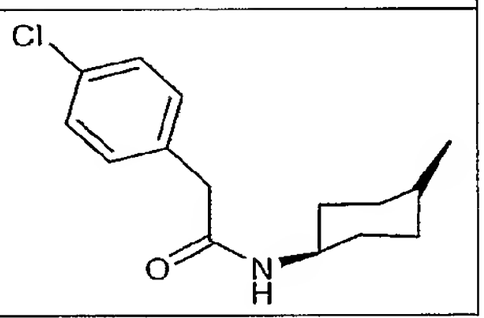
868		
869		
870		
871		
872		
873		

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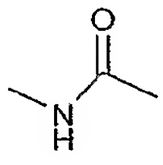
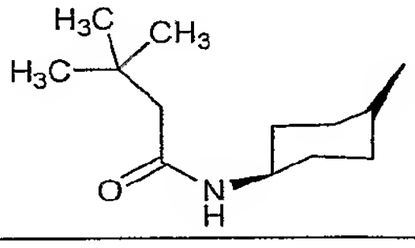
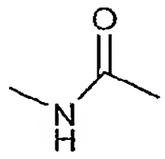
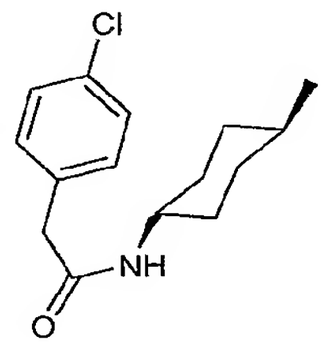
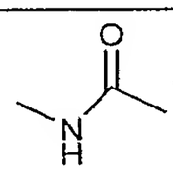
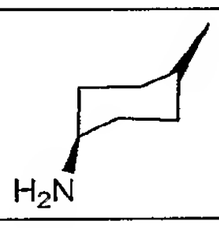
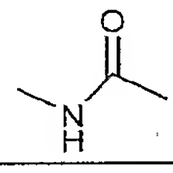
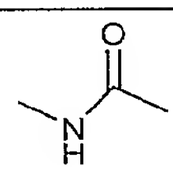
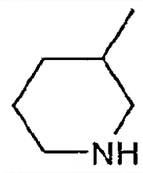
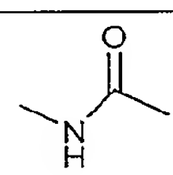
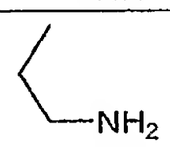
874		
875		
876		
877		
878		
879		

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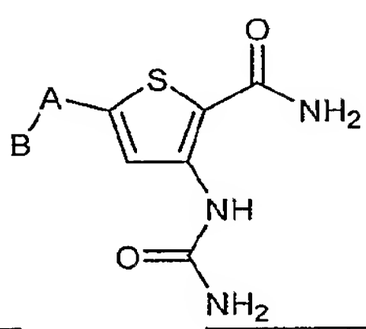
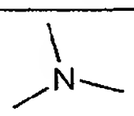
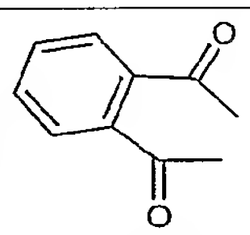
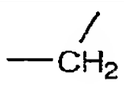
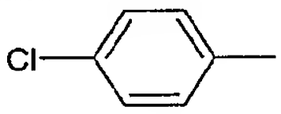


Ex.	-A-	B-
880		
881		

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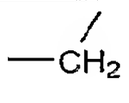
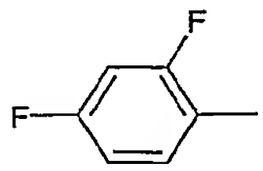
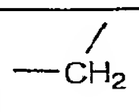
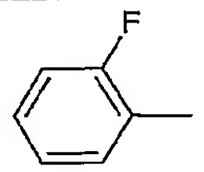
882		
883		

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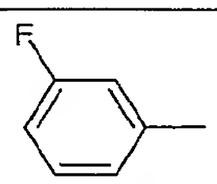
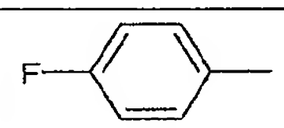
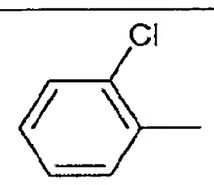
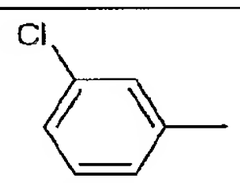
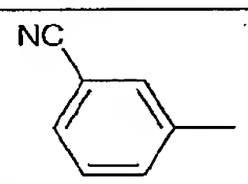
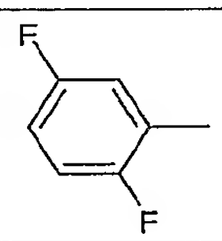
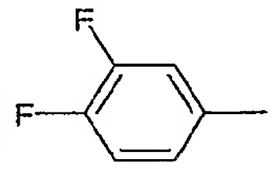
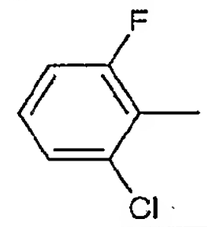
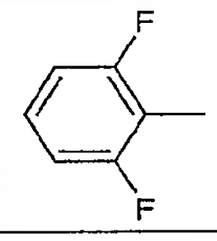
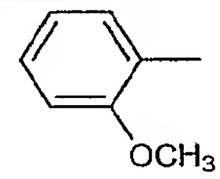
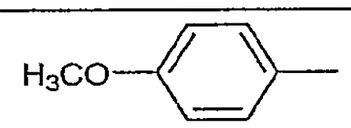
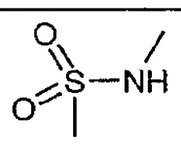
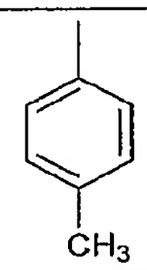
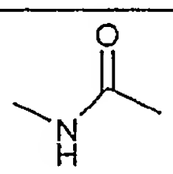
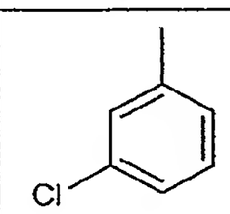
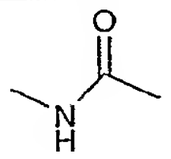
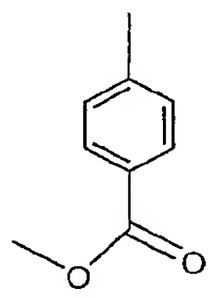
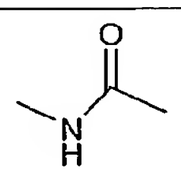
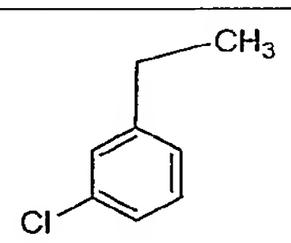
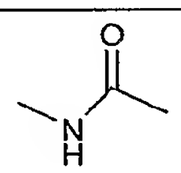
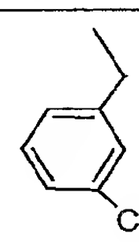
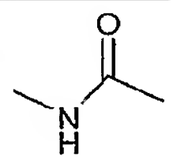
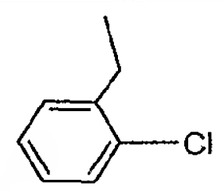
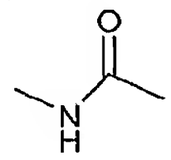
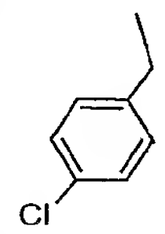
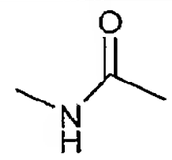
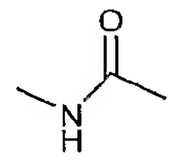
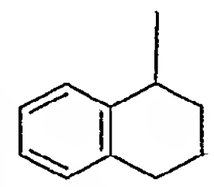
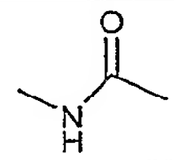
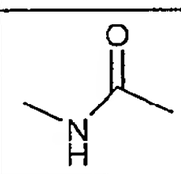
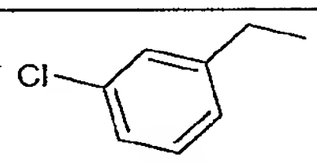
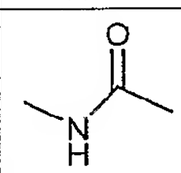
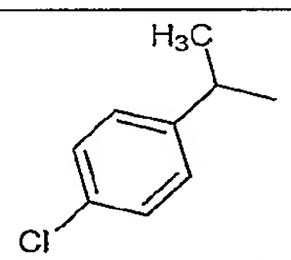
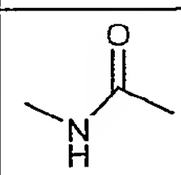
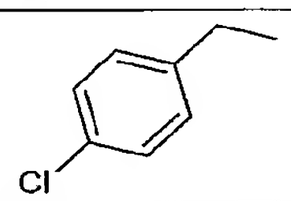
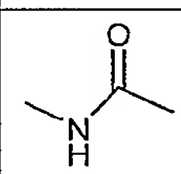
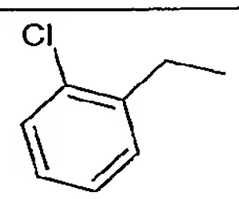
884	—CH2	
885	—CH2	
886	—CH2	
887	—CH2	
888	—CH2	
889	—CH2	
890	—CH2	
891	—CH2	
892	—CH2	
893	—CH2	
894	—CH2	
895		
896		

Ex.	-A-	B-
897		
898		
899		
900		
901		
902		
903		
904		—H
905		
906		
907		
908		

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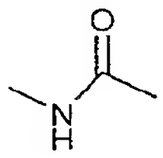
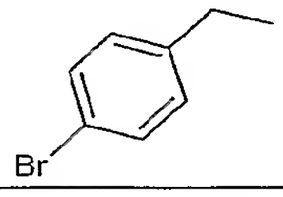
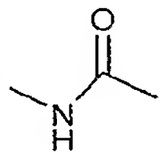
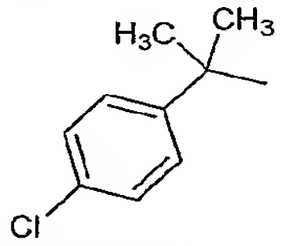
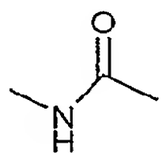
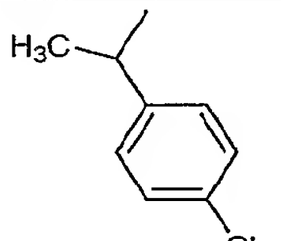
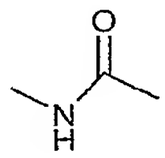
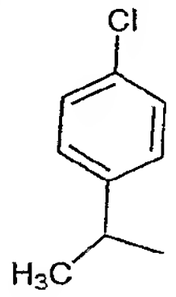
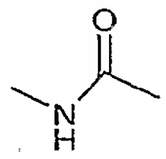
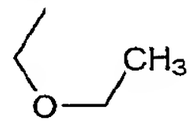
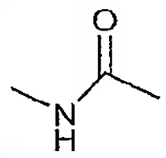
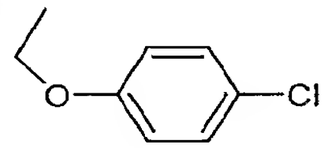
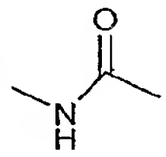
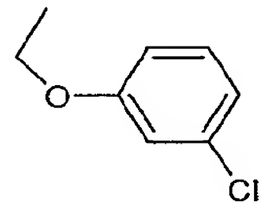
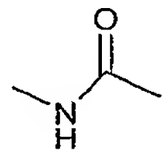
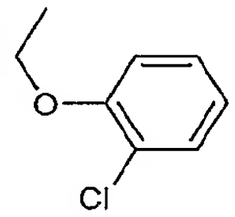
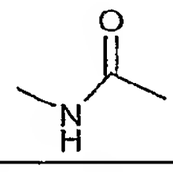
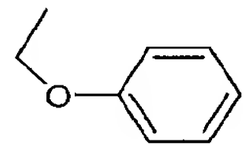
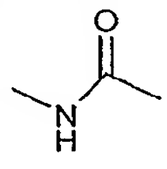
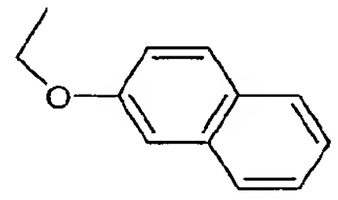
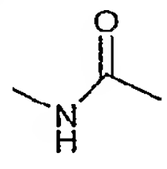
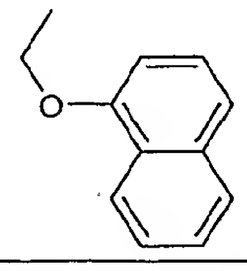
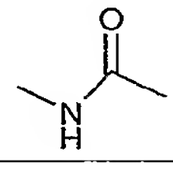
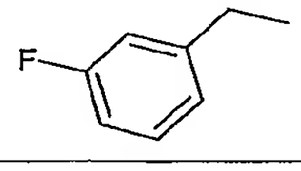
909		
910		
911		
912		
913		
914		
915		
916		
917		
918		
919		
920		

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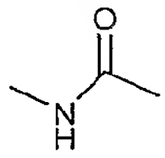
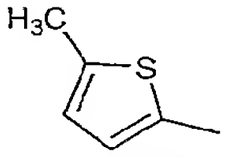
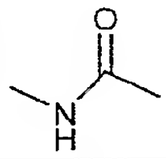
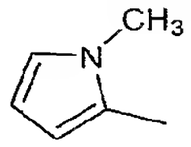
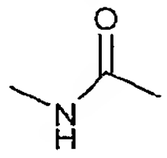
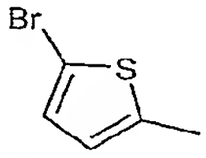
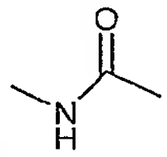
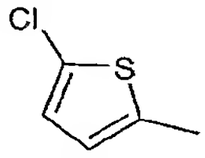
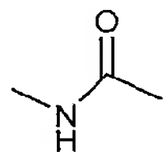
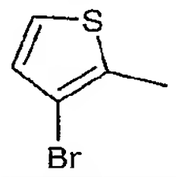
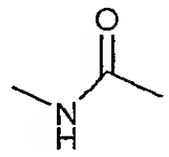
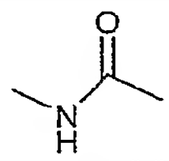
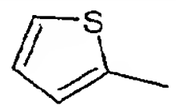
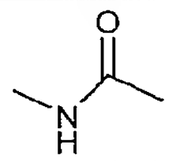
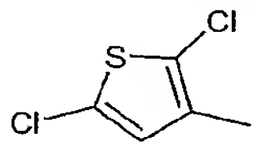
921		
922		
923		
924		
925		
926		
927		
928		
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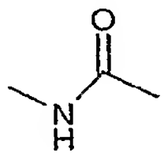
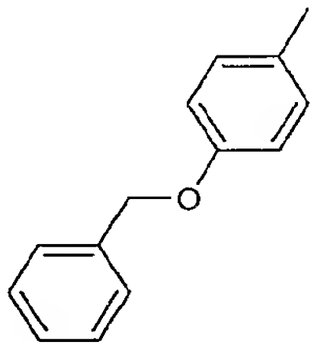
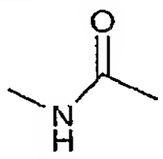
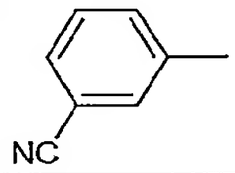
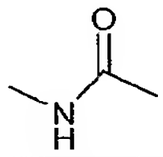
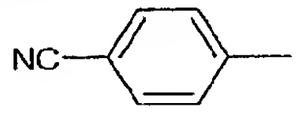
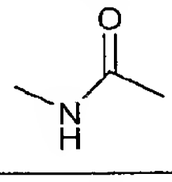
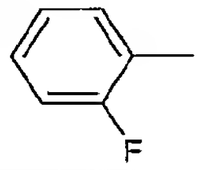
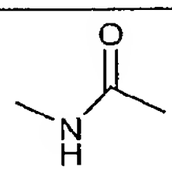
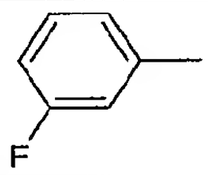
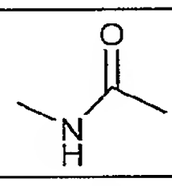
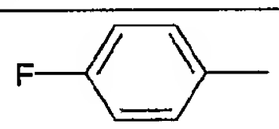
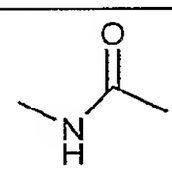
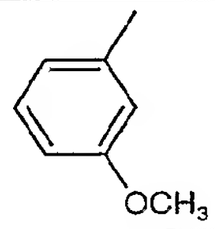
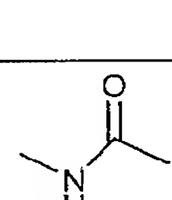
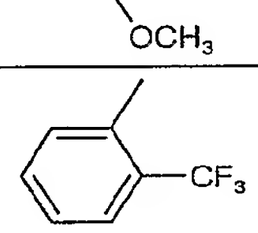
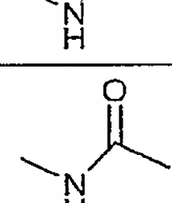
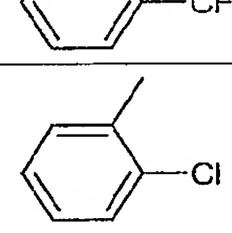
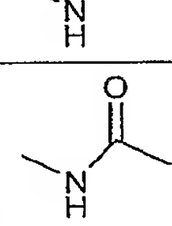
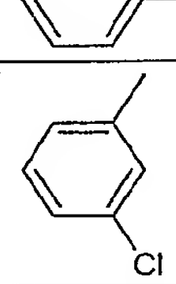
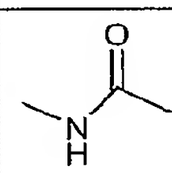
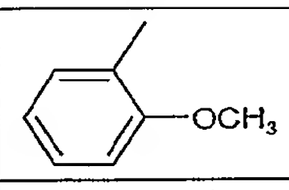
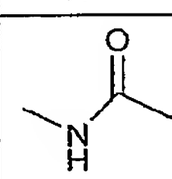
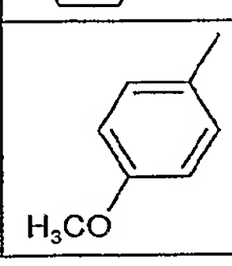
934		
935		
936		
937		
938		
939		
940		
941		
942		
943		
944		
945		

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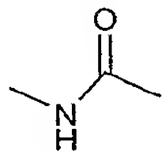
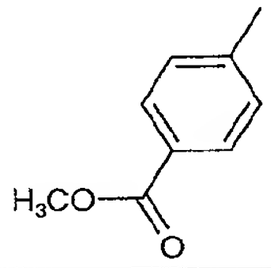
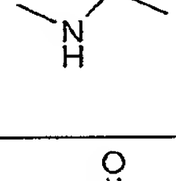
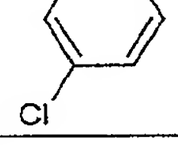
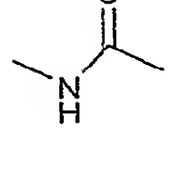
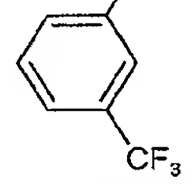
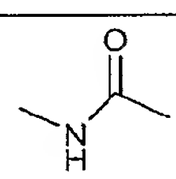
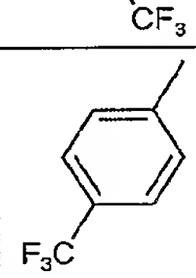
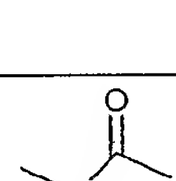
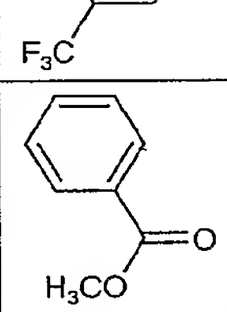
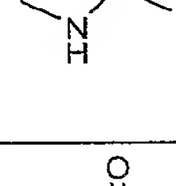
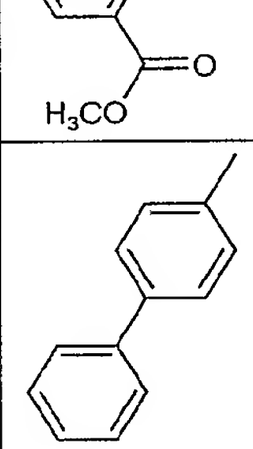
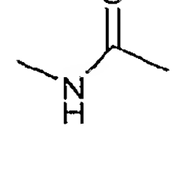
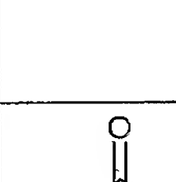
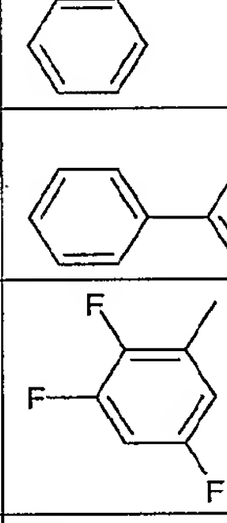
946		
947		
948		
949		
950		
951		
952		
953		
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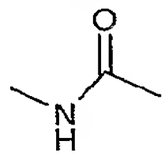
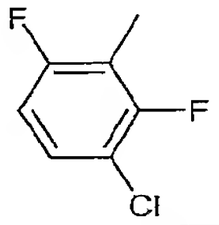
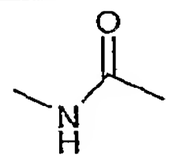
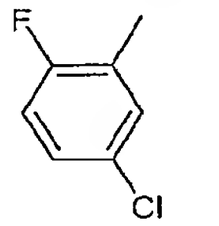
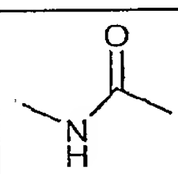
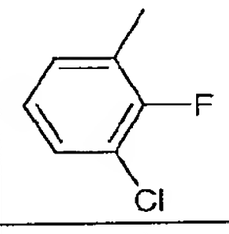
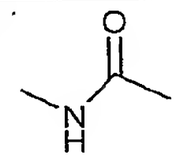
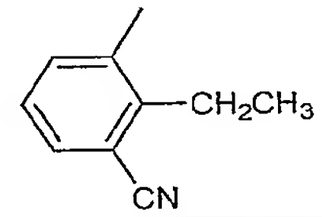
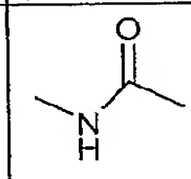
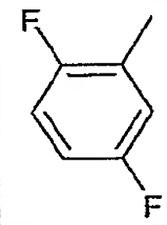
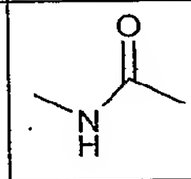
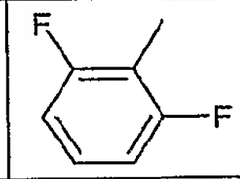
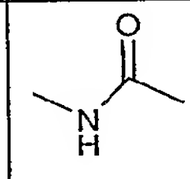
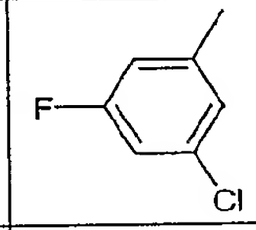
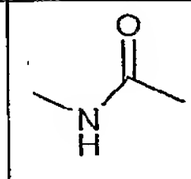
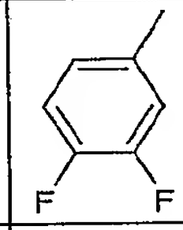
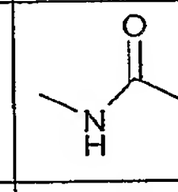
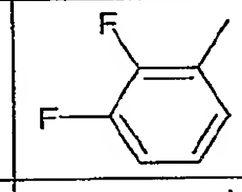
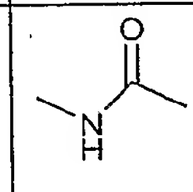
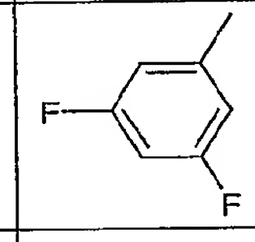
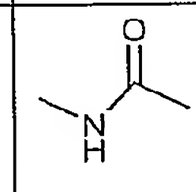
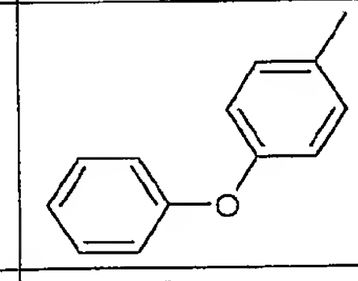
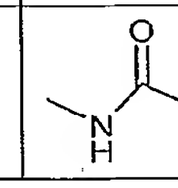
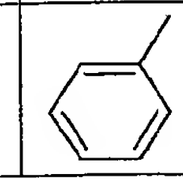
957		
958		
959		
960		
961		
962		
963		
964		
965		
966		
967		
968		

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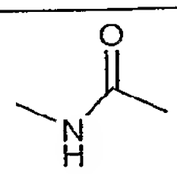
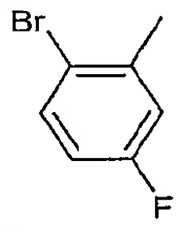
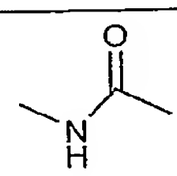
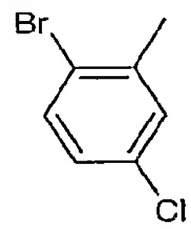
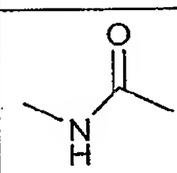
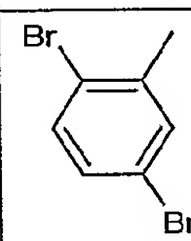
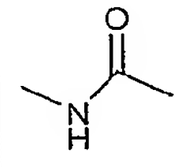
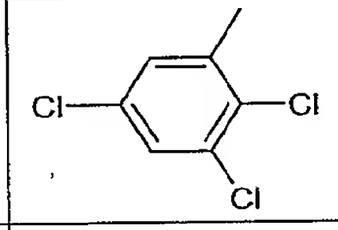
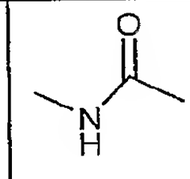
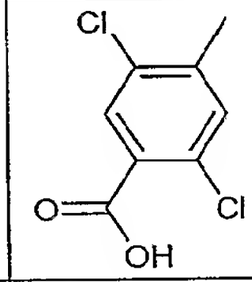
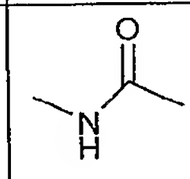
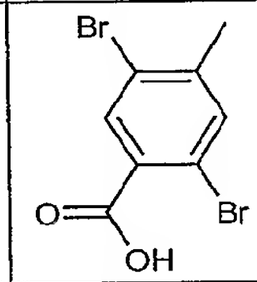
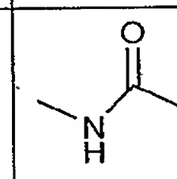
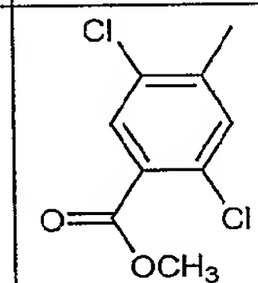
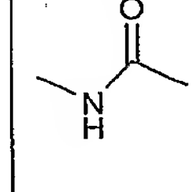
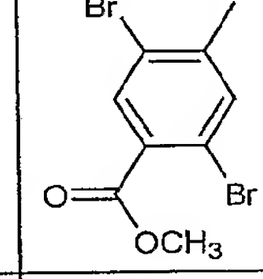
969		
970		
971		
972		
973		
974		
975		
976		
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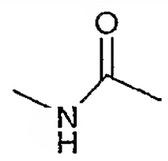
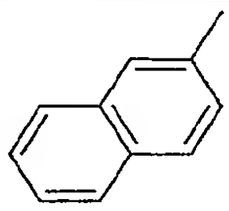
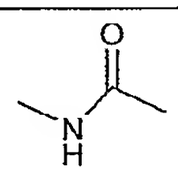
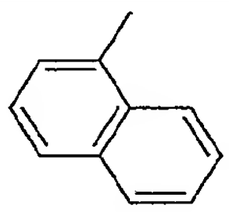
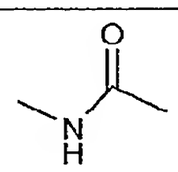
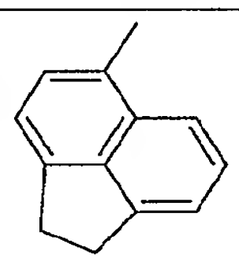
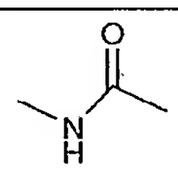
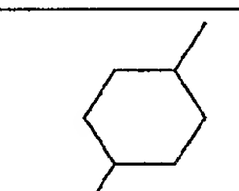
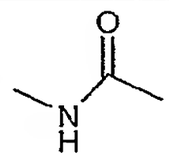
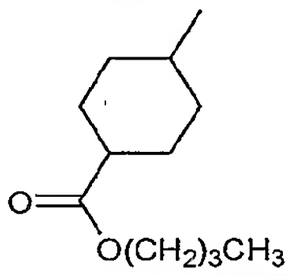
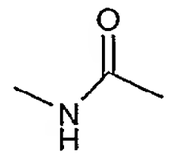
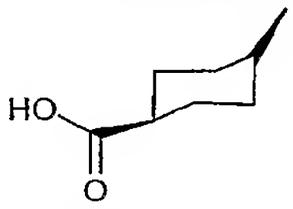
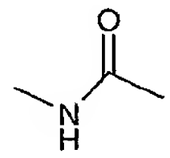
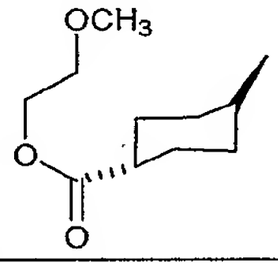
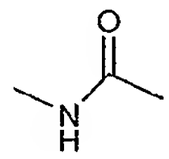
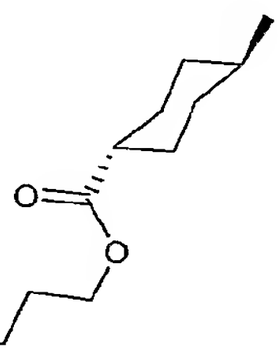
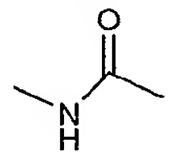
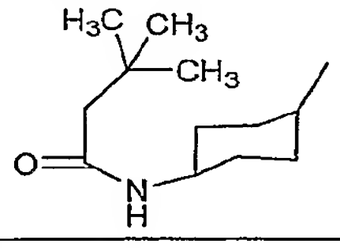
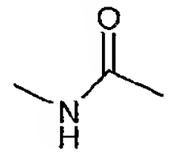
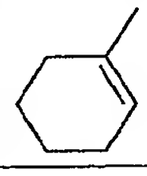
979		
980		
981		
982		
983		
984		
985		
986		
987		
988		

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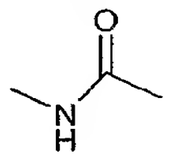
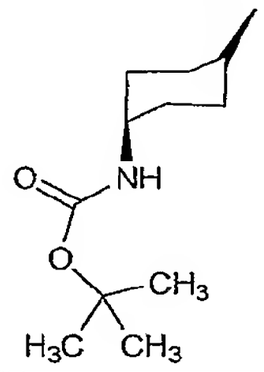
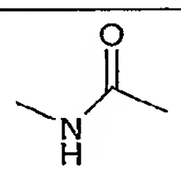
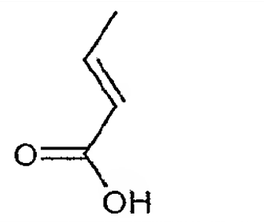
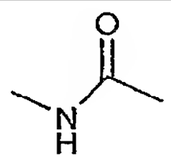
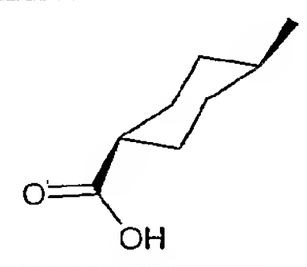
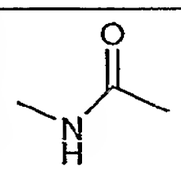
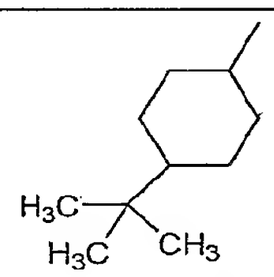
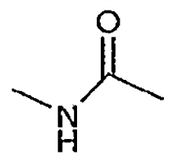
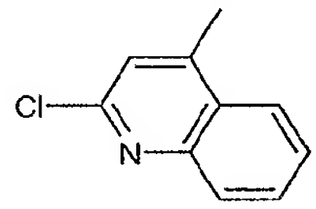
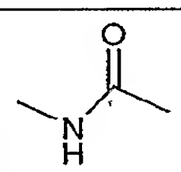
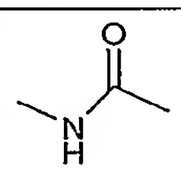
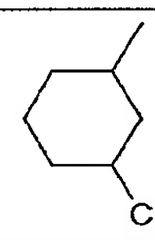
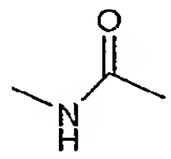
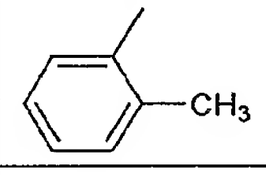
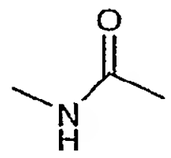
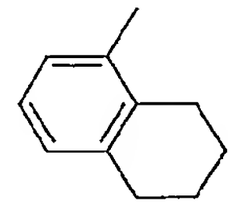
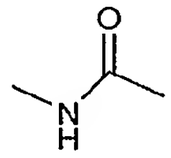
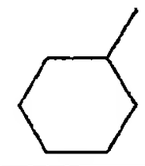
989		
990		
991		
992		
993		
994		
995		
996		
997		
998		
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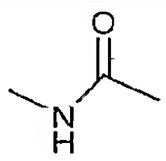
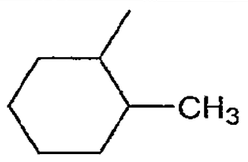
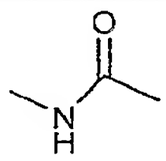
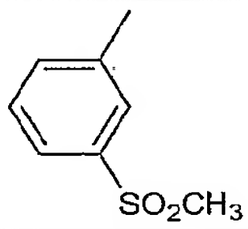
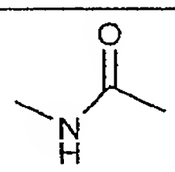
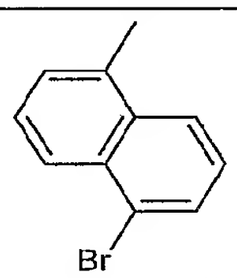
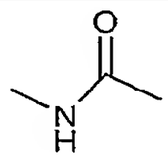
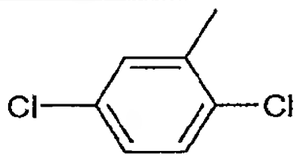
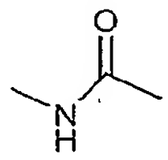
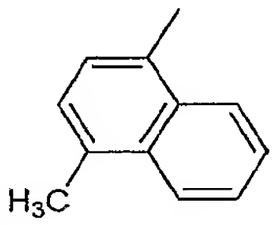
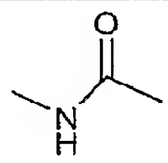
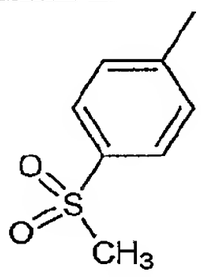
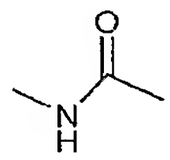
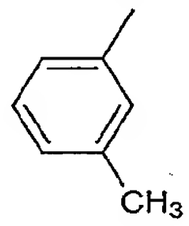
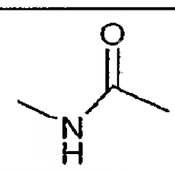
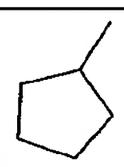
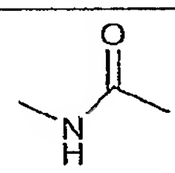
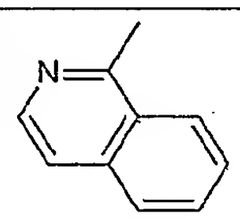
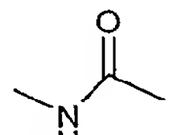
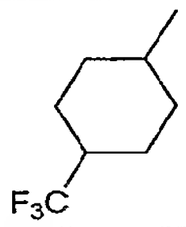
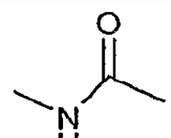
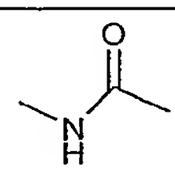
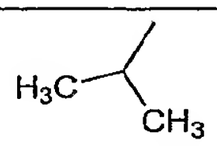
1000		
1001		
1002		
1003		
1004		
1005		
1006		
1007		
1008		
1009		
1010		
1011		

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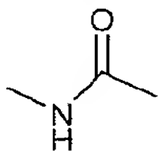
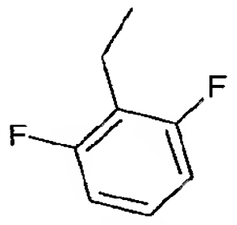
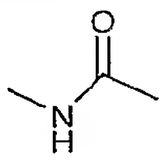
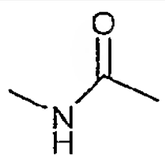
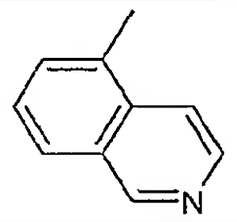
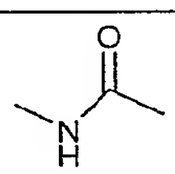
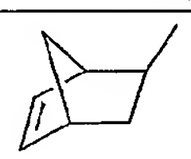
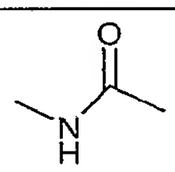
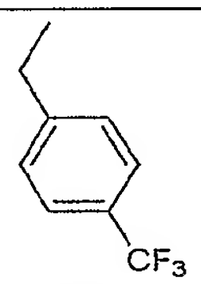
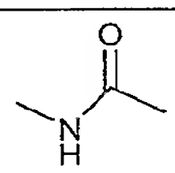
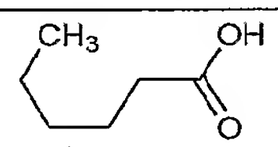
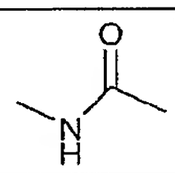
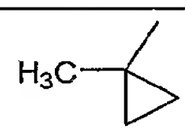
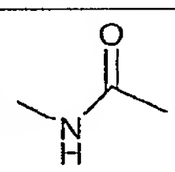
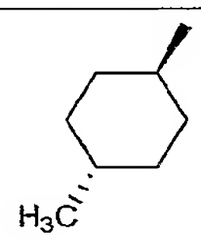
1012		
1013		
1014		
1015		
1016		
1017		
1018		
1019		
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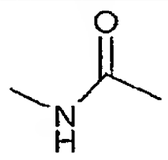
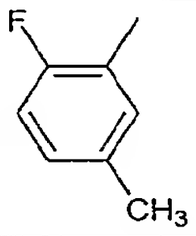
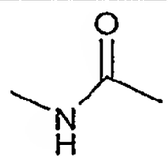
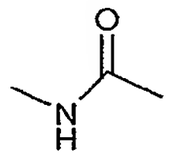
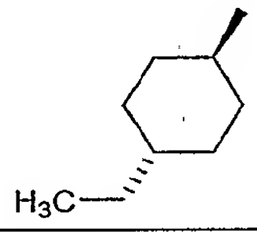
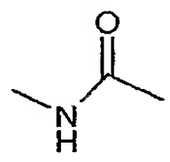
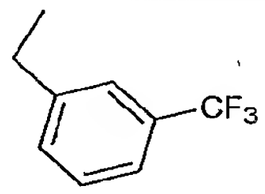
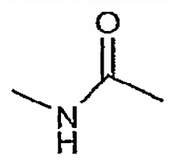
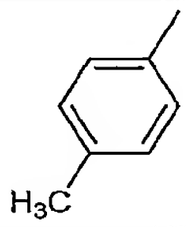
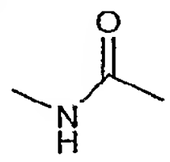
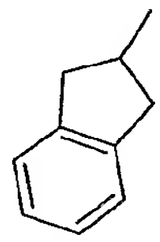
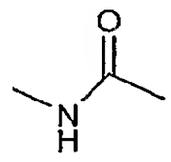
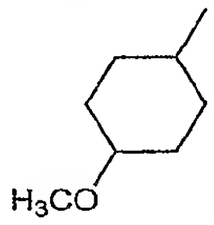
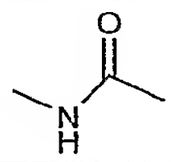
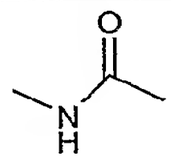
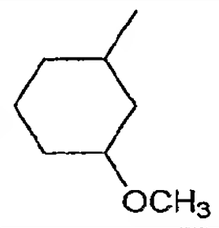
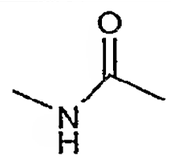
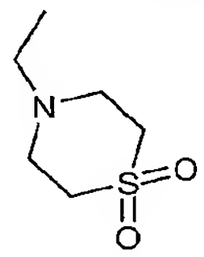
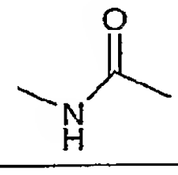
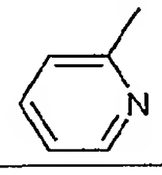
1024		
1025		
1026		
1027		
1028		
1029		
1030		
1031		
1032		
1033		
1034		

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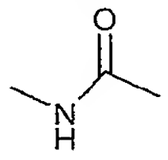
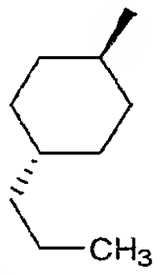
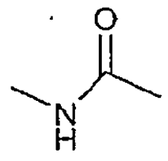
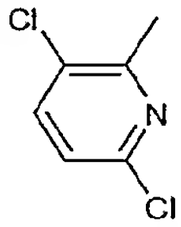
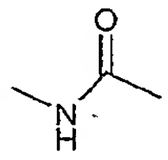
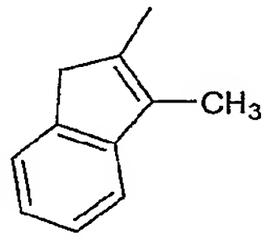
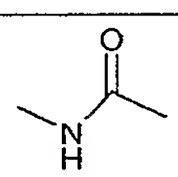
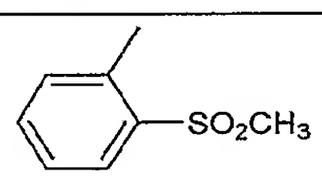
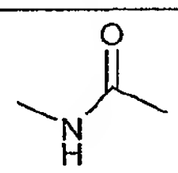
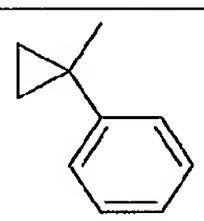
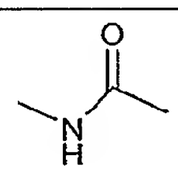
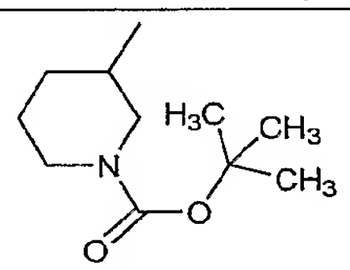
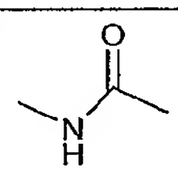
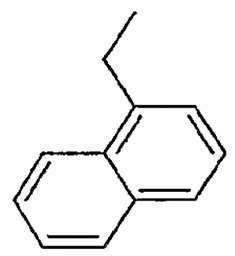
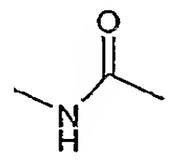
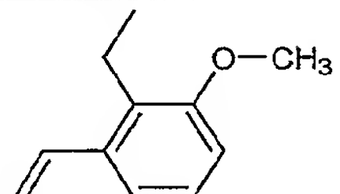
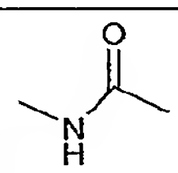
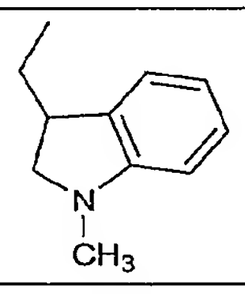
1035		
1036		
1037		
1038		
1039		
1040		
1041		
1042		
1043		
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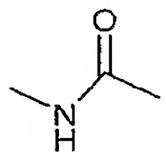
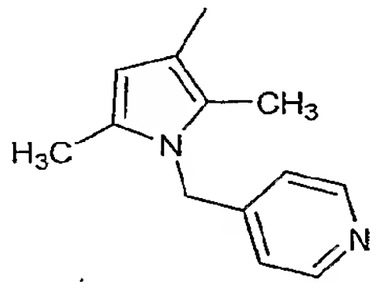
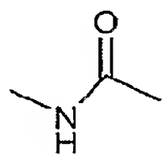
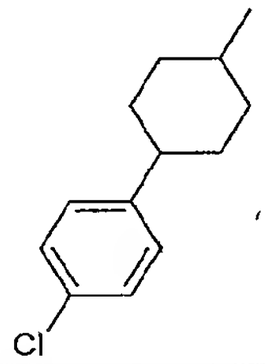
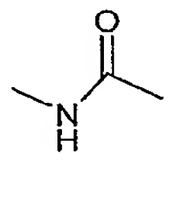
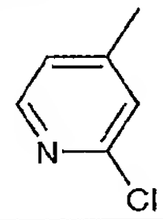
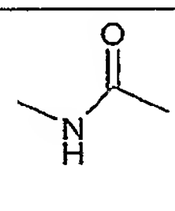
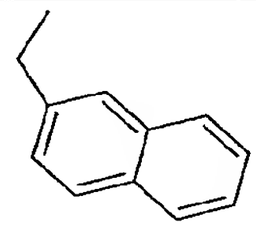
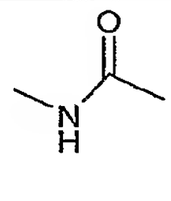
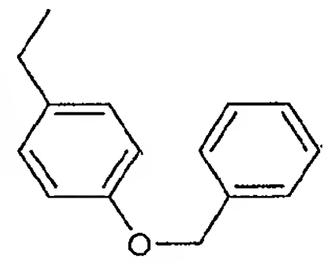
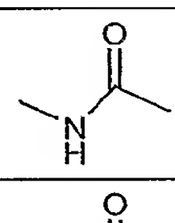
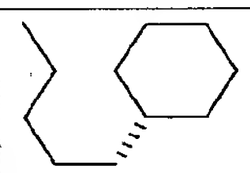
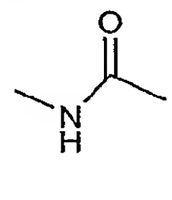
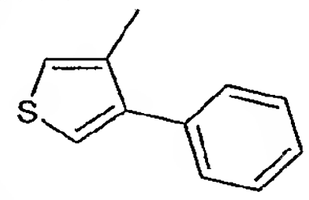
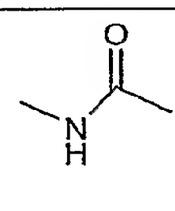
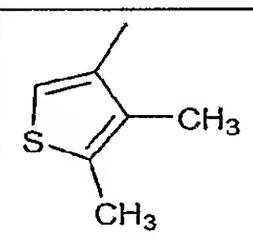
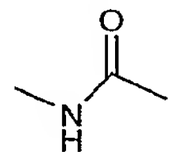
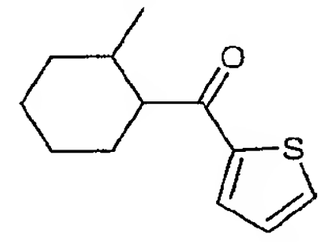
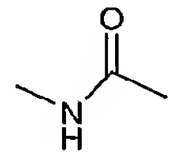
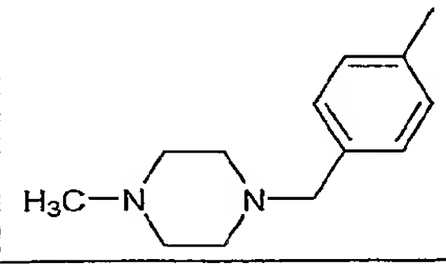
Ex.	-A-	B-
1045		
1046		
1047		
1048		
1049		
1050		
1051		
1052		
1053		
1054		

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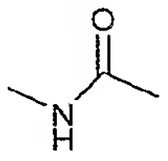
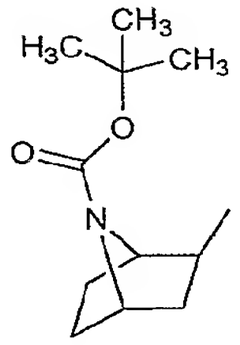
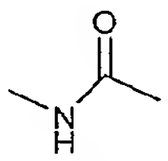
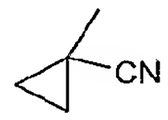
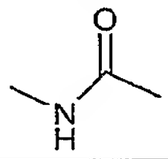
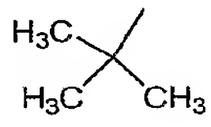
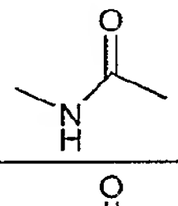
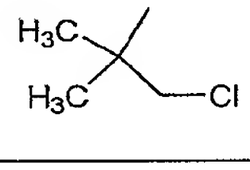
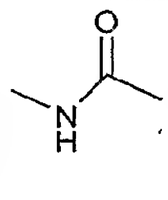
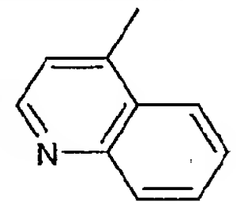
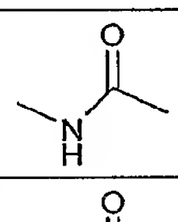
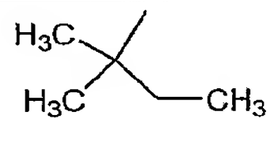
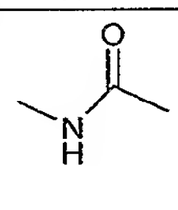
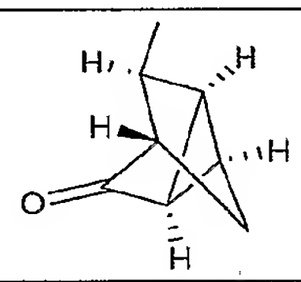
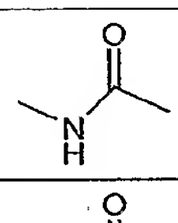
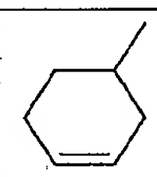
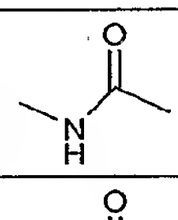
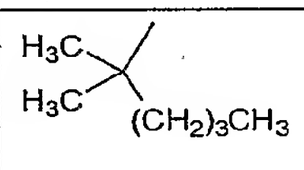
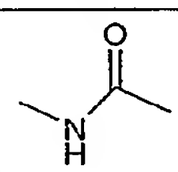
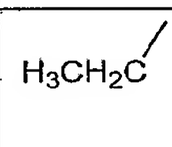
1055		
1056		
1057		
1058		
1059		
1060		
1061		
1062		
1063		
1064		
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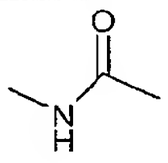
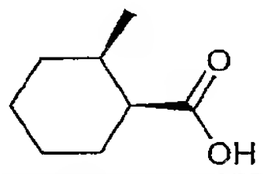
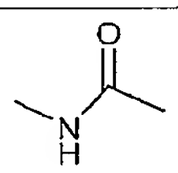
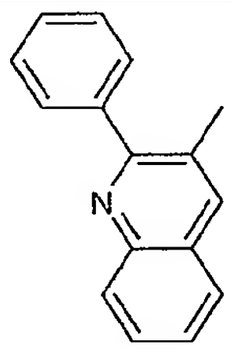
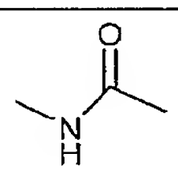
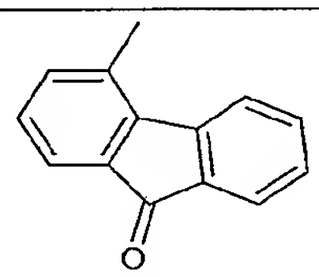
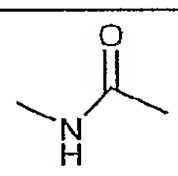
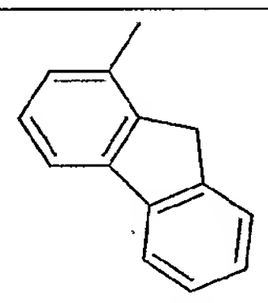
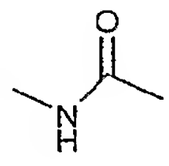
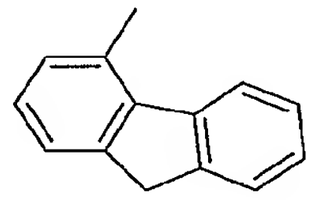
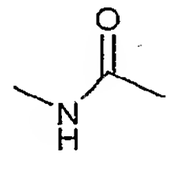
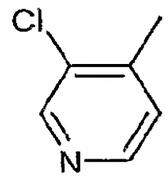
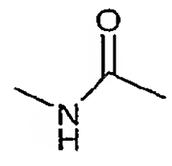
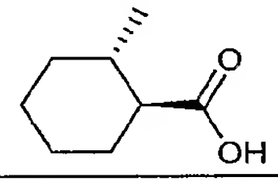
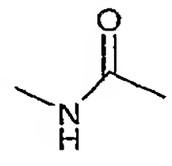
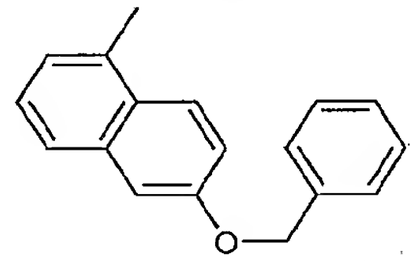
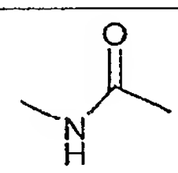
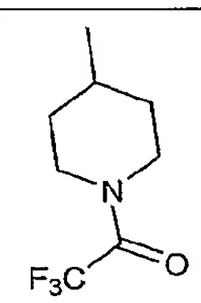
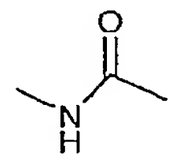
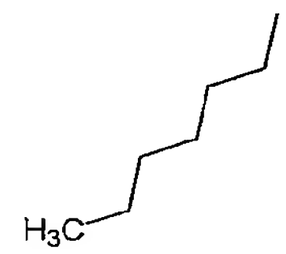
Ex.	-A-	B-
1068		
1069		
1070		
1071		
1072		
1073		
1074		
1075		
1076		
1077		

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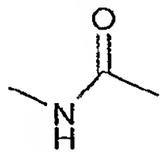
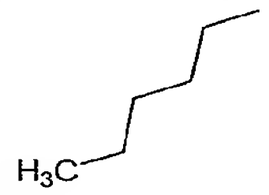
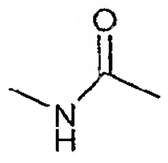
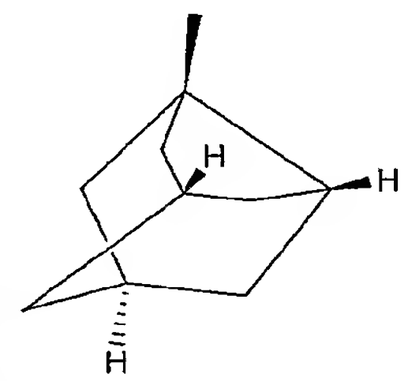
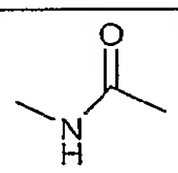
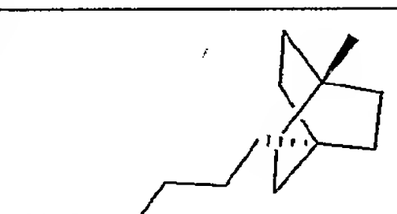
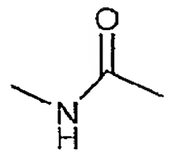
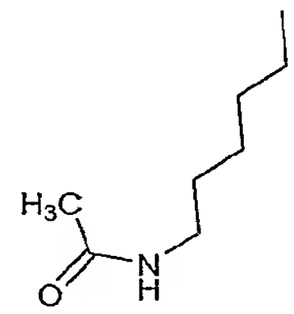
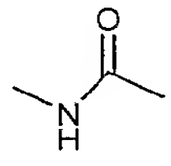
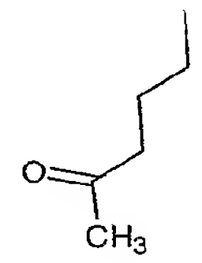
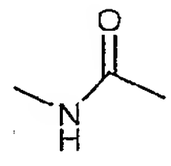
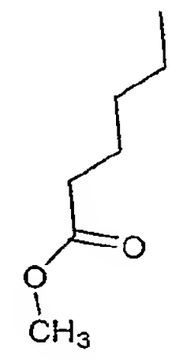
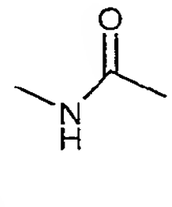
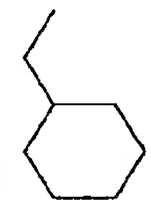
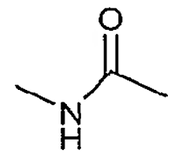
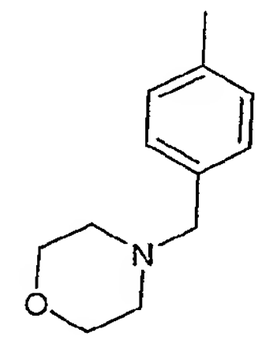
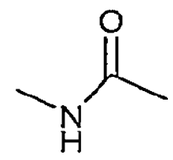
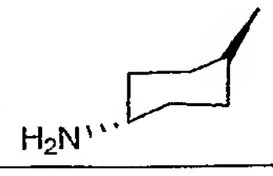
1078		
1079		
1080		
1081		
1082		
1083		
1084		
1085		
1086		

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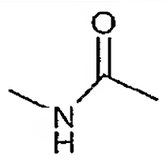
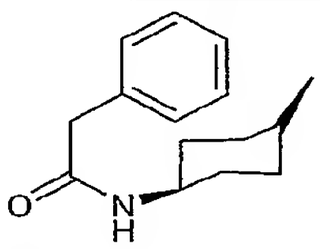
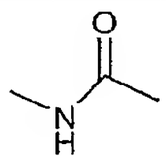
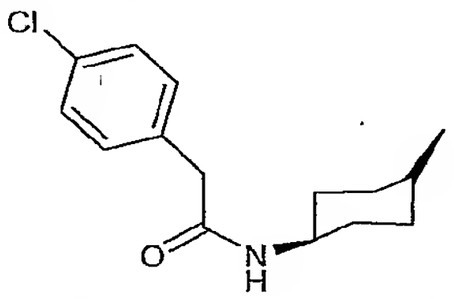
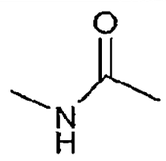
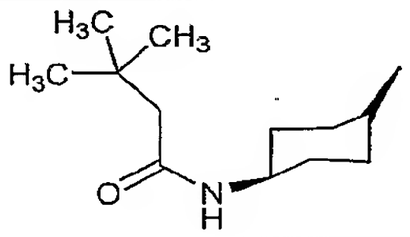
1087		
1088		
1089		

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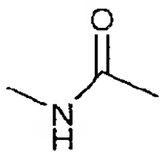
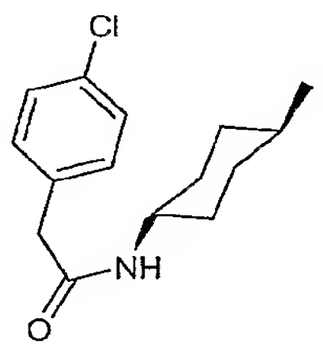
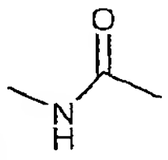
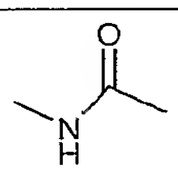
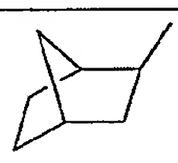
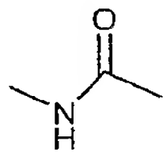
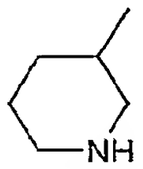
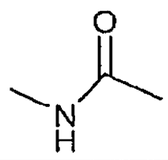
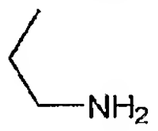
1090		
1091		
1092		
1093		
1094		

DEFINITIONS

[00198] The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical.

[00199] The term "halo" denotes halogen atoms such as fluorine, chlorine, bromine, or iodine.

[00200] The term "carbonyl", whether used alone or with other terms such as "alkylcarbonyl", denotes -(C=O)-.

[00201] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -CO_2H.

[00202] The term "sulfonyl," whether used alone or linked to other terms such as alkylsulfonyl, denotes the divalent radical -SO_2-.

[00203] The term "amido" when used by itself or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical.

[00204] The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively.

[00205] The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical.

[00206] The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical.

[00207] The terms "sulfamyl" or "sulfonamidyl" denotes a sulfonyl radical substituted with an amino radical, forming a sulfonamide (-SO_2NH_2). The amino radical may be substituted with alkyl and/or

aryl moieties to form, e.g., "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl," and "N-alkyl-N-arylsulfamyl" radicals.

[00208] The term "amidino" denotes a $-C(=NH)NH_2$ radical.

[00209] The term "cyanoamidino" denotes a $-C(=N-CN)NH_2$ radical.

[00210] The term "alkyl," used alone or within other terms such as "haloalkyl" and "alkylsulfonyl," embraces linear or branched radicals having one to about twenty carbon atoms. More preferred are "lower alkyl" radicals having one to about eight carbon atoms. Examples of alkyl radicals include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl, and t-butyl), pentyl (including n-pentyl and isoamyl), hexyl, octyl and the like.

[00211] The term "cycloalkyl" embraces radicals having three to ten carbon atoms, and includes monocyclic, bicyclic, and tricyclic radicals. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, decahydronaphthyl, octahydroindyl, octahydropentalene, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, and bicyclo[4.2.2]decyl.

[00212] The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an alkylcarbonyl radical is acetyl.

[00213] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of an alkylthio radical is methylthio (CH_3S-).

[00214] The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-S(=O)-$ radical. An example of an alkylsulfinyl radical is methylsulfinyl ($CH_3S(=O)-$).

[00215] The term "alkylsulfonyl" embraces alkyl radicals as defined above attached to a divalent sulfonyl radical, $-SO_2-$.

[00216] The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals.

[00217] The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical.

[00218] The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals.

[00219] The term "carboxyalkyl" embraces radicals having a carboxyl moiety attached to an alkyl radical.

[00220] The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihaloalkyl radicals may have two of the same halo atoms or a combination of different halo radicals; polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

[00221] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms, any of which may be substituted with one or more hydroxyl radicals.

[00222] The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively.

[00223] The term "alkoxy" embraces linear or branched oxy-containing alkyl radicals having one to about ten carbon atoms. Examples of "alkoxy" radicals include methoxy and butoxy.

[00224] The term "alkoxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms substituted by one or more alkoxy radicals each having one to about ten carbon atoms.

[00225] "Alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals.

[00226] The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such alkoxycarbonyl radicals include methoxycarbonyl and t-butoxycarbonyl.

[00227] The term "alkoxycarbonylalkyl" embraces radicals having alkoxycarbonyl moiety, as defined above substituted to an alkyl radical. Examples of such alkoxycarbonylalkyl radicals include methoxycarbonylethyl ($-(CH_2)_2(O=)COCH_3$) and t-butoxycarbonylethyl ($-(CH_2)_2(O=)COC(CH_3)_3$).

[00228] The term "alkylaminoalkyl" embraces aminoalkyl radicals wherein the nitrogen atom is substituted with an alkyl radical.

[00229] The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical.

[00230] The term "alkenyl," used alone or within other terms such as "haloalkenyl," embraces unsaturated linear or branched radicals having two to about twenty carbon atoms and containing at least one carbon-carbon double bond. Examples of alkenyl radicals include ethenyl, propenyl butenyl, pentenyl, and the like.

[00231] The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms and containing at least one carbon-carbon double bond, and includes monocyclic, bicyclic, and tricyclic radicals. Examples of cycloalkenyl radicals include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, decahydronaphthenyl, hexahydroindenyl, hexahydropentalenyl, bicyclo[2.1.0]pentenyl, bicyclo[1.1.1]pentenyl, bicyclo[2.1.1]hexenyl, bicyclo[2.2.1]heptenyl, bicyclo[3.1.1]heptenyl, bicyclo[3.2.1]octenyl, bicyclo[2.2.2]octenyl, and bicyclo[4.2.2]decenyl.

[00232] The term "alkynyl," used alone or within other terms such as "haloalkynyl," embraces unsaturated linear or branched radicals having two to about twenty carbon atoms and containing at least one carbon-carbon triple bond. Examples of alkynyl radicals include ethynyl, propynyl butynyl, pentynyl, and the like.

[00233] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein at least one of the rings is aromatic, and wherein such rings may be attached together in a pendant manner or may be fused. Examples of aryl radicals include phenyl, naphthyl, tetrahydronapthyl, indyl, and biphenyl. Aryl moieties, alone or in combination, may be optionally substituted by one or more substituents selected from the group consisting of amino, halo, cyano, hydroxyl, alkyl, alkoxy, and carboxyl.

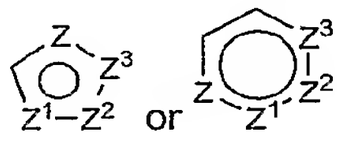
[00234] The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl.

[00235] The term "arylsulfonyl" embraces aryl radicals as defined above attached to a sulfonyl radical.

[00236] The term "acyl," whether used alone or within a term such as "acylamino," denotes a radical provided by the residue after removal of hydroxyl from an organic acid.

[00237] The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino ($CH_3C(=O)NH-$).

[00238] The term "heterocyclic" or "heterocycle" means a saturated or unsaturated mono- or multi-ring carbocyclic system wherein one or more carbon atoms in the system are replaced by nitrogen, sulfur, phosphorous, and/or oxygen. The term "heterocyclic" embraces "heteroaryl" groups, which means a carbocyclic aromatic system containing one, two, or three rings wherein at least one of the rings is aromatic, wherein such rings may be attached together in a pendant manner or may be fused, and wherein one or more carbon atoms in the system are replaced by nitrogen, sulfur, phosphorous, and/or oxygen. "Heterocyclic" includes, for example, the following structures:

[00239]  or

[00240] wherein Z, Z^1, Z^2, and Z^3 are independently carbon, sulfur, phosphorous, oxygen, or nitrogen, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not oxygen or sulfur when attached to another Z atom by a double bond or when attached to another oxygen or sulfur atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is carbon. For example, the term "heterocyclyl" embraces each of the following groups, although this listing is not meant to limit the definition to these groups only: furanyl; thienyl; pyrrolyl; 2-isopyrrolyl; 3-isopyrrolyl; pyrazolyl; 2-isoimidazolyl; 1,2,3-triazolyl; 1,2,4-triazolyl; 1,2-dithiolyl; 1,3-dithiolyl; 1,2,3-oxathiolyl; isoxazolyl; oxazolyl; thiazolyl; isothiazolyl; 1,2,3-oxadiazolyl; 1,2,4-oxadiazolyl; 1,2,5-oxadiazolyl; 1,3,4-oxadiazolyl; 1,2,3,4-oxatriazolyl; 1,2,3,5-oxatriazolyl; 1,2,3-dioxazolyl; 1,2,4-dioxazolyl; 1,3,2-dioxazolyl; 1,3,4-dioxazolyl; 1,2,5-oxathiazolyl; 1,3-oxathiolyl; 1,2-pyranyl; 1,4-pyranyl; 1,2-pyranonyl; 1,4-pyranonyl; 1,2-dioxinyl; 1,3-dioxinyl; pyridyl; pyridazyl; pyrimidyl; pyrazinyl; piperazyl; 1,3,5-triazinyl; 1,2,4-triazinyl; 1,2,3-triazinyl; 1,2,4-oxazinyl; 1,3,2-oxazinyl; 1,3,6-oxazinyl; 1,2,6-oxazinyl; 1,4-oxazinyl; o-isoxazinyl; p-isoxazinyl; 1,2,5-oxathiazinyl; 1,4-oxazinyl; o-isoxazinyl; p-isoxazinyl; 1,2,5-oxathiainzyl; 1,2,6-oxathiainzyl; 1,4,2-oxadiainzyl; 1,3,5,2-oxadiainzyl; morpholino; azepinyl; oxepinyl; thiepinyl; 1,2,4-diazepinyl; benzofuranyl; isobenzofuranyl; benzothiofuranyl; isobenzothiofuranyl; indolyl; indoleninyl; 2-isobenzazolyl; 1,5-pyrindinyl; pyrano[3,4-b]pyrrolyl; isoindazolyl; indoxazinyl; benzoxazolyl; anthranilyl; 1,2-benzopyranyl; quinolyl; isoquinolyl; cinnolyl; quinazolyl; naphthyridyl; pyrido[3,4-b]pyridyl; pyrido[3,2-b]pyridyl; pyrido[4,3-b]pyridyl; 1,3,2-benzoxazyl; 1,4,2-benzoxazyl; 2,1,3-benzoxazyl; 3,1,4-benzoxazyl; 1,2-benzoisoxazyl; 1,4-benzoisoxazyl; carbazolyl; xanthenyl; acridinyl; purinyl; thiazolidyl; piperidyl; pyrrolidyl; 1,2-dihydroazinyl; 1,4-dihydroazinyl; 1,2,3,6-tetrahydro-1,3-diazinyl; perhydro-1,4-diazinyl; 1,2-thiapyranyl; and 1,4-thiapyranyl. Heterocyclic moieties, alone or in combination, may be optionally substituted by one or more substituents selected from the group consisting of amino, halo, cyano, hydroxyl, alkyl, alkoxy, and carboxyl.

[00241] The term "heteroaryl" also embraces radicals where heterocyclic radicals are fused with aryl radicals as defined herein. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

[00242] The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl.

[00243] The terms benzyl and phenylmethyl are interchangeable.

[00244] The phrases "combination therapy", "co-administration", "administration with", or "co-therapy", in defining the use of a selective IKK-2 inhibitory agent in combination with another therapeutic agent such as another analgesic agent, is intended to embrace administration of each agent in a sequential manner in a regimen that may provide beneficial effects of the drug combination, and is

intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule or dosage device having a fixed ratio of these active agents or in multiple, separate capsules or dosage devices for each agent, where the separate capsules or dosage devices can be taken together contemporaneously, or taken within a period of time sufficient to receive a beneficial effect from both of the constituent agents of the combination.

[00245] The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of, or who has pain, inflammation and/or any one of the known inflammation-associated disorders. The subject is typically a human subject.

[00246] The phrase "therapeutic combination" as used herein refers to the combination of two or more therapeutic compounds and, optionally, one or more pharmaceutically acceptable carrier used to provide dosage forms that produce a beneficial effect of each therapeutic compound in the subject at the desired time, whether the therapeutic compounds are administered substantially simultaneously, or sequentially.

[00247] The phrase "therapeutically effective" as used herein refers to an amount of a therapeutic compound, or amounts of combined therapeutic compounds in combination therapy. The amount or combined amounts achieve one or more of the goals of preventing, inhibiting, reducing or eliminating the inflammation or inflammation-related disease or condition. A "therapeutically-effective" amount of each agent in a combination therapy is expected to be less than an amount used in treatment using agent by itself, thus while avoiding adverse side effects typically associated with alternative therapies, namely higher dose monotherapy of each agent by itself.

[00248] The terms "treating" or "to treat" means to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms in a subject. The term "treatment" includes alleviation, elimination of causation of or prevention of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described above.

[00249] Pharmaceutically acceptable salts of the compounds of Formula I include the acid addition and base salts thereof.

[00250] Suitable acid addition salts are formed from acids that form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[00251] Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

[00252] Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

[00253] Pharmaceutically acceptable salts of compounds of Formula I may be prepared by one or more of three methods: (i) by reacting the compound of Formula I with the desired acid or base; (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of Formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or

base; or (iii) by converting one salt of the compound of Formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column. All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

[00254] The compounds of the invention may exist in both unsolvated and solvated forms. The term "solvate" is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term "hydrate" is employed when said solvent is water.

[00255] Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized; or non-ionized. For a review of such complexes, see Haleblian, J. Pharm. Sci., **64(8)**, 1269-1288 (1975).

[00256] Hereinafter all references to compounds of Formula I include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[00257] The compounds of the invention include compounds of Formula I as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of Formula I.

[00258] As indicated, so-called prodrugs of the compounds of Formula I are also within the scope of the invention. The term "prodrug" refers to a compound that is a drug precursor which, following administration to a subject and subsequent absorption, is converted to an active species *in vivo* via some process, such as a metabolic process. Other products from the conversion process are easily disposed of by the body. The more preferred prodrugs are those involving a conversion process that produces products that are generally accepted as safe.

[00259] Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of Formula I with certain moieties known to those skilled in the art as "pro-moieties."

[00260] Some examples of prodrugs in accordance with the invention include: (i) where the compound of Formula I contains a carboxylic acid functionality (-CO_2H), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of Formula I is replaced by C_1-C_8 alkyl; (ii) where the compound of Formula I contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of Formula I is replaced by C_1-C_6 alkanoyloxymethyl; and (iii) where the compound of Formula I contains a primary or secondary amino functionality (-NH_2 or -NHR where R $\neq$H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of Formula I is/are replaced by C_1-C_{10} alkanoyl.

[00261] Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

[00262] Moreover, certain compounds of Formula I may themselves act as prodrugs of other compounds of Formula I.

[00263] Also included within the scope of the invention are metabolites of compounds of Formula I, that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include: (i) where the compound of Formula I contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3 \rightarrow -CH_2OH$); (ii) where the compound of Formula I contains an alkoxy group, an hydroxy derivative thereof ($-OR \rightarrow -OH$); (iii) where the compound of Formula I contains a tertiary amino group, a secondary amino derivative thereof ($-NR^aR^b \rightarrow -NHR^a$ or $-NHR^b$); (iv) where the compound of Formula I contains a secondary amino group, a primary derivative thereof ($-NHR \rightarrow -NH_2$); (v) where the compound of Formula I contains a phenyl moiety, a phenol derivative thereof ($-Ph \rightarrow -PhOH$); and (vi) where the compound of Formula I contains an amide group, a carboxylic acid derivative thereof ($-CONH_2 \rightarrow -COOH$).

[00264] Compounds of Formula I containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of Formula I contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ("tautomerism") can occur. This can take the form of proton tautomerism in compounds of Formula I containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[00265] Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of Formula I, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartrate or dl-arginine.

[00266] Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

[00267] Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (chiral HPLC).

[00268] Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of Formula I contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

[00269] Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2 to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

[00270] Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art.

[00271] The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of Formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

[00272] Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

[00273] Certain isotopically-labeled compounds of Formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium (^{3}H) and ^{14}C are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[00274] Substitution with heavier isotopes such as deuterium (^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[00275] Substitution with positron-emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[00276] Isotopically-labeled compounds of Formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[00277] Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, or d_6-DMSO.

[00278] Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

[00279] Generally, the compounds of the invention may be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

[00280] The compounds of the invention may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). For example, compounds of Formula I may be used in co-therapies, partially or completely, in place of other conventional antiinflammatory therapies, such as together with other IKK-2 inhibitors, steroids, NSAIDs, COX-2 selective inhibitors, matrix metalloproteinase inhibitors, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

[00281] Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art.

[00282] The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

[00283] Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

[00284] Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

[00285] The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, Expert Opinion in Therapeutic Patents, **11(6)**, 981-986 (2001).

[00286] For tablet dosage forms, depending on dose, the drug may make up from 1 to 80 wt.% of the dosage form, more typically from 5 to 60 wt.% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 to 25 wt.%, preferably from 5 to 20 wt.% of the dosage form.

[00287] Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

[00288] Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 to 5 wt.% of the tablet, and glidants may comprise from 0.2 to 1 wt.% of the tablet.

[00289] Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 to 10 wt.%, preferably from 0.5 to 3 wt.% of the tablet.

[00290] Other possible ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

[00291] Exemplary tablets contain up to about 80% drug, from about 10 to about 90 wt.% binder, from about 0 to about 85 wt.% diluent, from about 2 to about 10 wt.% disintegrant, and from about 0.25 to about 10 wt.% lubricant.

[00292] Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before

tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

[00293] Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of Formula I, a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabilizer or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

[00294] The compound of Formula I may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 to 80 wt.%, more typically from 20 to 50 wt.%, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 wt.% of the solutes. Alternatively, the compound of Formula I may be in the form of multiparticulate beads.

[00295] The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 wt.%, more typically in the range 30 to 80 wt.%.

[00296] Other possible ingredients include anti-oxidants, colorants, flavorings and flavor enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

[00297] Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

[00298] Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release.

[00299] Suitable modified release formulations for the purposes of the invention are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma et al., Pharmaceutical Technology On-line, **25(2)**, 1-14 (2001). The use of chewing gum to achieve controlled release is described in PCT Publication No. WO 00/35298.

[00300] The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

[00301] Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

[00302] The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

[00303] The solubility of compounds of Formula I used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

[00304] Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(dl-lactic-coglycolic)acid (PGLA) microspheres.

[00305] The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated; see, e.g., Finnin and Morgan, J Pharm Sci, **88(10)**, 955-958 (1999).

[00306] Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

[00307] Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release.

[00308] The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

[00309] The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00310] Prior to use in a dry powder or suspension formulation, the drug product is micronized to a size suitable for delivery by inhalation (typically less than 5 μM). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00311] Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

[00312] A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1 µg to 20 mg of the compound of the invention per actuation and the actuation volume may vary from 1 to 100 µL. A typical formulation may comprise a compound of Formula I, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

[00313] Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

[00314] Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release.

[00315] In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 20 to 1000 μg of the compound of Formula I. The overall daily dose will typically be in the range 100 μg to 10 mg which may be administered in a single dose or, more usually, as divided doses throughout the day, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

[00316] The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

[00317] Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release.

[00318] The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g., absorbable gel sponges, collagen) and non-biodegradable (e.g., silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

[00319] Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- or programmed-release.

[00320] The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

[00321] Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e.,

as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, such as those described in PCT Publication No. WO 98/55148.

[00322] Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

[00323] Such kits comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of Formula I in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

[00324] Such kits are particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

[00325] The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the inflammation or inflammation related disorder, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 1000 mg, preferably in the range of about 7.0 to 350 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 0.5 to 30 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day. In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

[00326] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[00327] These dosages are based on an average human subject having a weight of about 60 to 70 kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

[00328] For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

[00329] "dba" is dibenzylideneacetone.

[00330] "DMF" is N,N-dimethylformamide.

[00331] "DMSO" is dimethylsulfoxide.

[00332] "ESI" is electrospray ionization Mass spectrometry.

[00333] "HATU" is O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

[00334] "HBTU" is O-benzotriazolo-1-yl)-N,N,N', N'-tetramethyluronium.

[00335] "HRMS" is high resolution mass spectrometry.

[00336] "NMR" is nuclear magnetic resonance.

[00337] "Ac" is acetyl.

[00338] "OAc" is acetate.

[00339] "Ph" is phenyl.

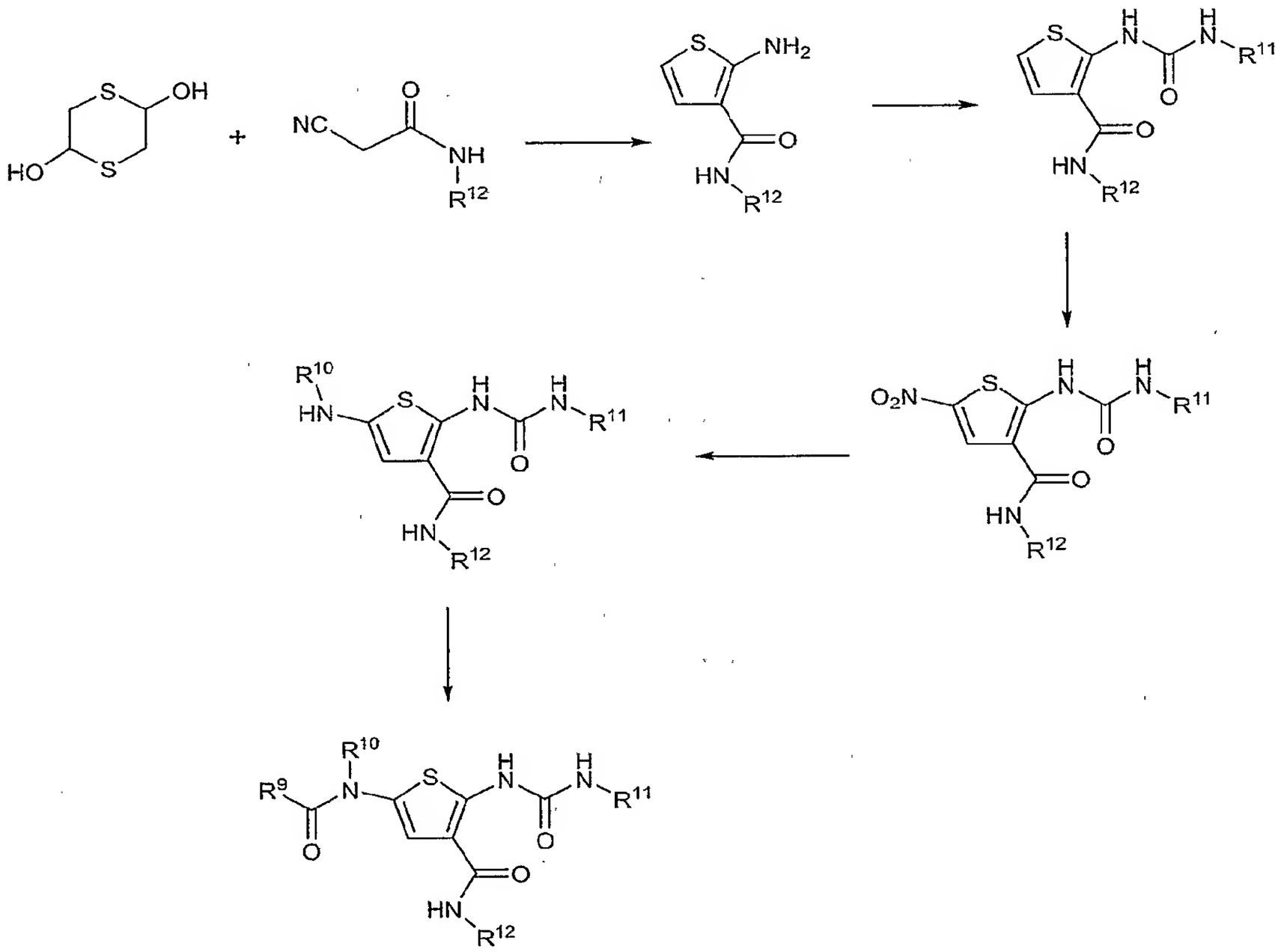
[00340] "i.d." is inner diameter.

REACTION SCHEMES

[00341] Compounds of Formula I may be prepared according to the reaction schemes set forth below.

Scheme I

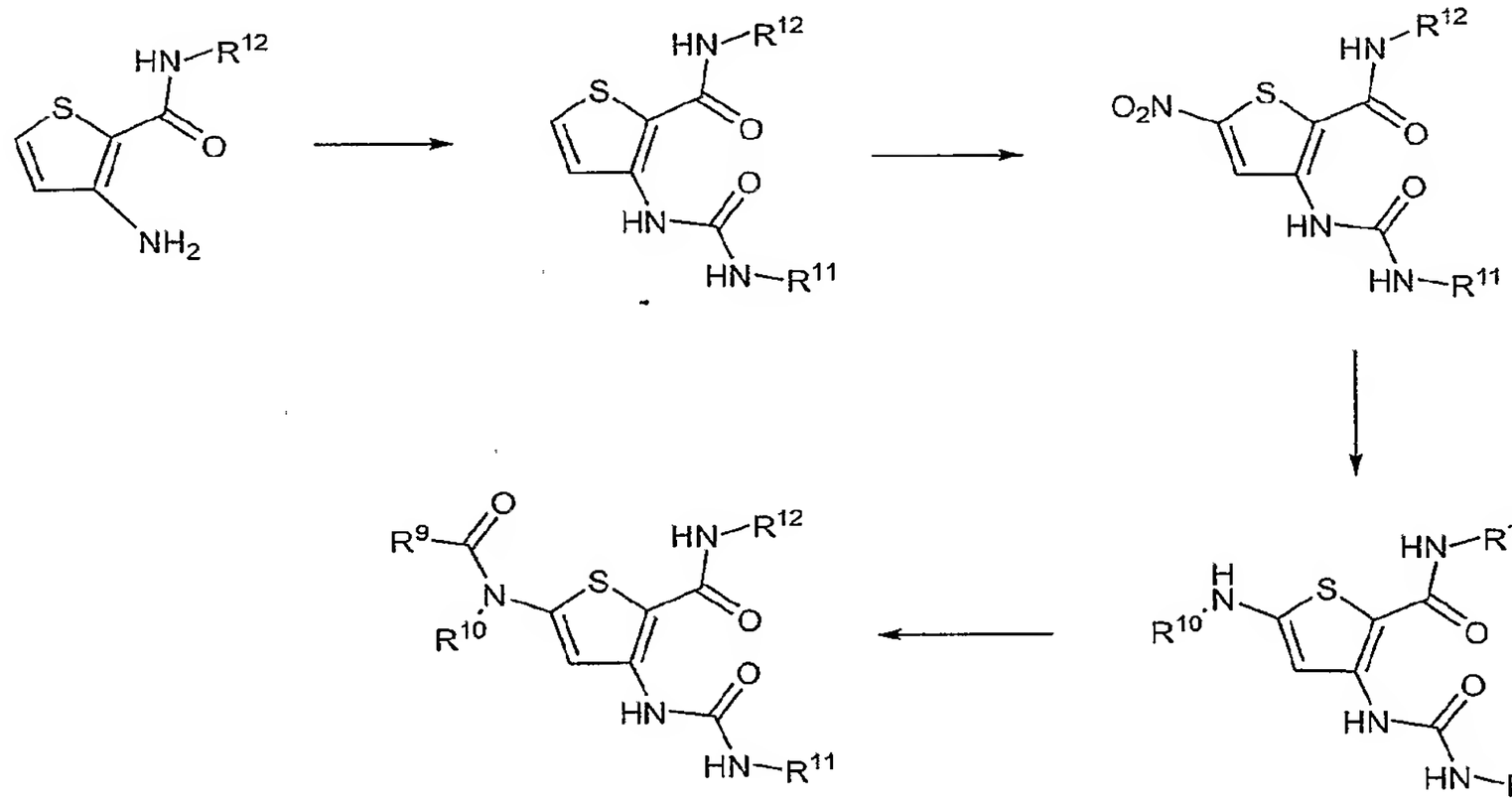
Synthesis of 2-ureido-3-carboxamido thiophene-5-carboxamides



[00342] Condensation of 2,5-dihydroxy-1,4-dithiane with an appropriate cyanoacetamide gives a 2-aminothiophene-3-carboxamide. Conversion to the 2-ureido-3-carboxamidothiophene is achieved by the standard methods for urea formation, such as the use of sodium cyanate in acetic acid. Careful nitration using nitric acid in acetic anhydride produces the 5-nitro derivative. Reduction of the nitro derivative with tin in hydrochloric acid produces the 2-ureido-3-carboxamido-5-aminothiophene as a salt. Finally, the 5-amide is produced by reaction with carboxylic acids using standard coupling reagents such as HBTU tetrafluoroborate and tertiary amine as base.

Scheme II

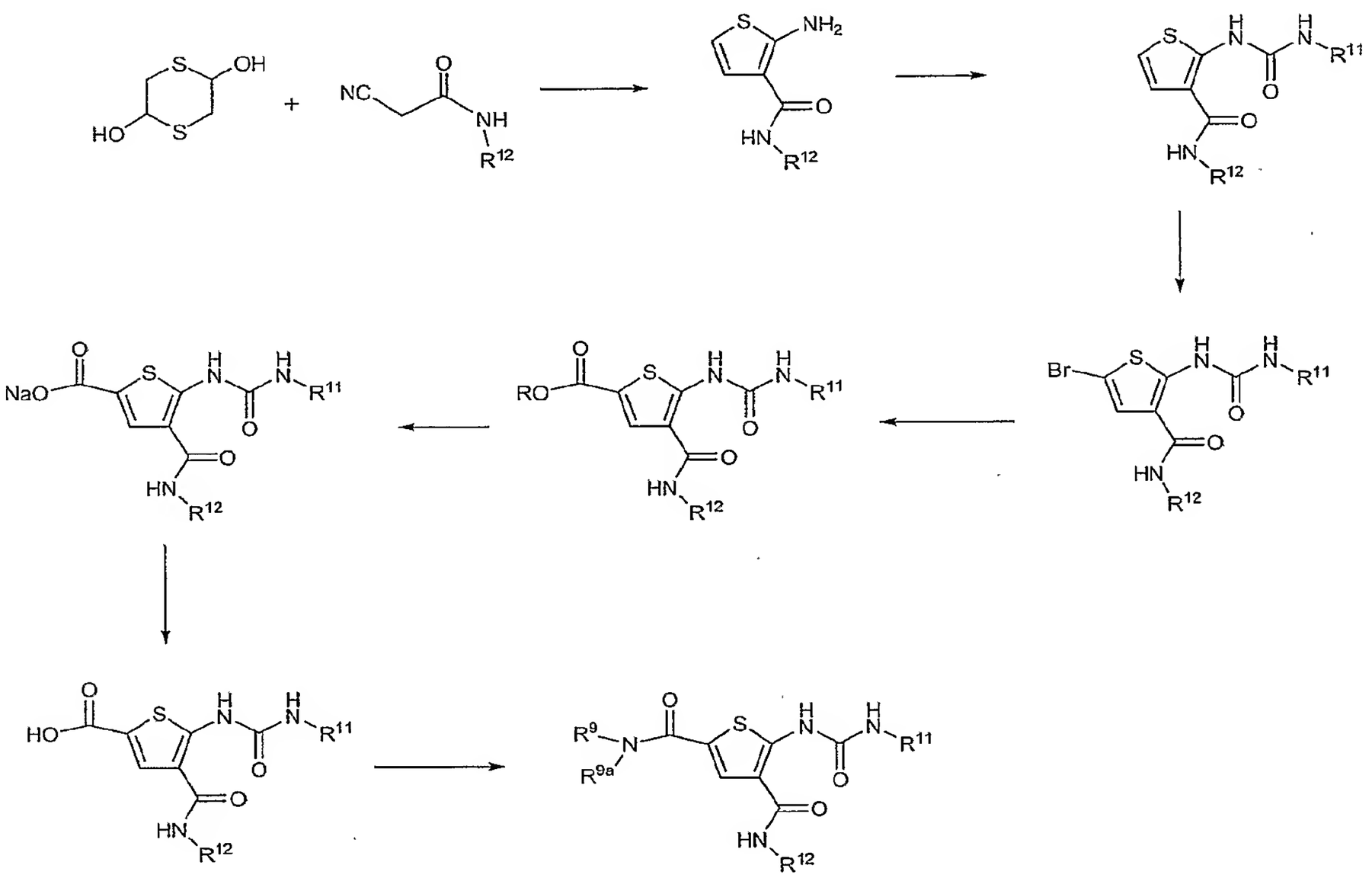
Synthesis of 2-carboxamido-3-ureido thiophene-5-amides



[00343] Starting from commercially available 2-carboxamido-3-aminothiophene, the 2-carboxamido-3-ureidothiophene is prepared via conventional procedures for urea formation such as reaction with sodium cyanate in acetic acid. Nitration may produce a mixture of isomers from which the desired 5-nitro compound can be separated. Reduction of the nitro derivative can be achieved for example by reaction with tin in hydrochloric acid. The resulting ammonium salt is treated under standard coupling conditions with a carboxylic acid and an appropriate coupling reagent, such as HBTU tetrafluoroborate, in the presence of a tertiary amine base.

Scheme IIIA

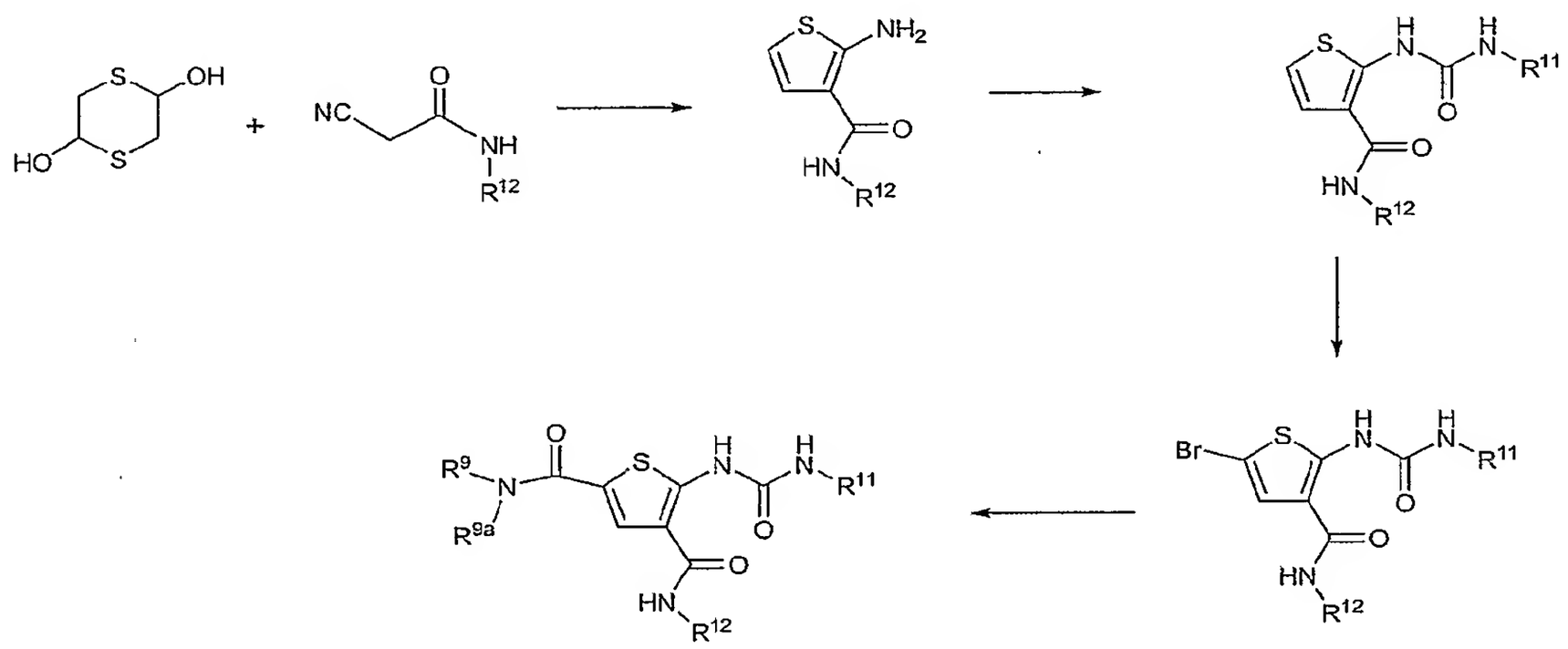
Synthesis of 2-ureido-3-carboxamido thiophene-5-carboxamides from esters via carbonylation



[00344] Condensation of 2,5-dihydroxy-1,4-dithiane with an appropriate cyanoacetamide gives a 2-aminothiophene-3-carboxamide. Conversion to the 2-ureido-3-carboxamidothiophene is achieved by the standard methods for urea formation, such as the use of sodium cyanate in acetic acid. Bromination can be effected by, for example, bromine in acetic acid to produce the desired 5-bromo derivative. Carbonylation of the 5-bromo derivative using carbon monoxide, with a transition metal catalyst, such as a palladium compound, for example palladium (II) acetate, optionally in the presence of an added ligand, for example, a phosphine, such as 1,1'-bis(diphenylphosphino)ferrocene in an alcohol, such as methanol, as solvent gives an ester, such as methyl 2-ureido-3-carboxamido-thiophene-5-carboxylate. This ester is hydrolyzed by conventional methods, as, for example, by saponification, giving, in this instance, a carboxylate salt, which can be isolated, or directly transformed into the carboxylic acid by treatment with acid. This 2-ureido-3-carboxamido-thiophene-5-carboxylic acid can be coupled with amines using certain coupling agents such as HBTU tetrafluoroborate to produce 2-ureido-3-carboxamido-5-carboxamidothiophenes. Heating may be necessary depending on the type of amine being coupled, as in the case of certain anilines.

Scheme IIIB

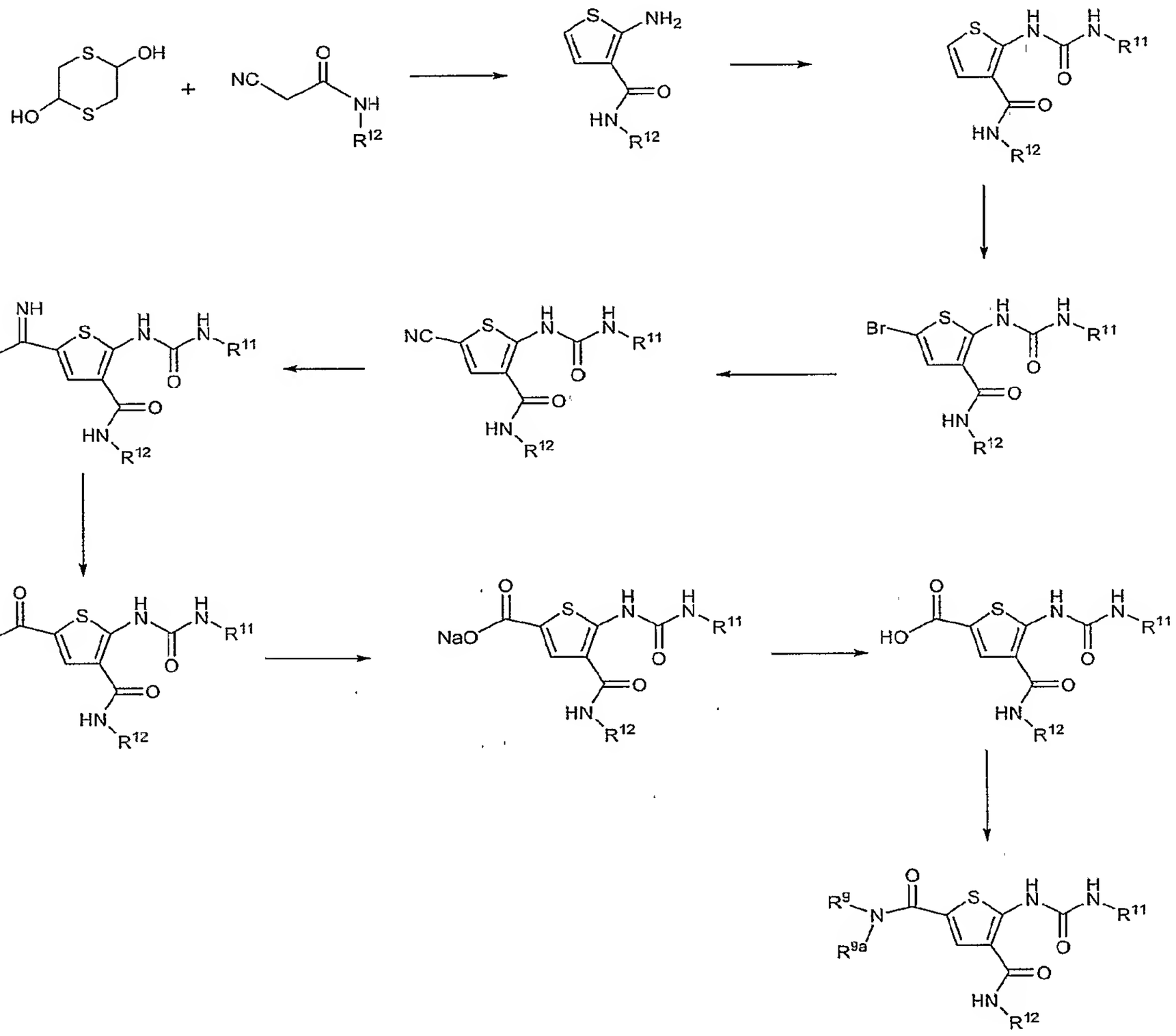
Synthesis of 2-ureido-3-carboxamido thiophene-5-carboxamides via direct carbonylation to amides



[00345] Condensation of 2,5-dihydroxy-1,4-dithiane with an appropriate cyanoacetamide gives the 2-aminothiophene-3-carboxamide. Conversion to the 2-ureido-3-carboxamidothiophene is achieved by the standard methods for urea formation, such as the use of sodium cyanate in acetic acid. Bromination can be effected by, for example, bromine in acetic acid to produce the desired 5-bromo derivative. Carbonylation of the 5-bromo derivative using carbon monoxide, with a transition metal catalyst, such as a palladium compound, for example palladium (II) acetate, optionally in the presence of an added ligand, for example, a phosphine, such as 1,1'-bis(diphenylphosphino)ferrocene in an appropriate solvent, such as DMF, containing the desired amine and a tertiary amine, gives an amide such as 2-ureido-3-carboxamido-5-carboxamidothiophene.

Scheme IIIC

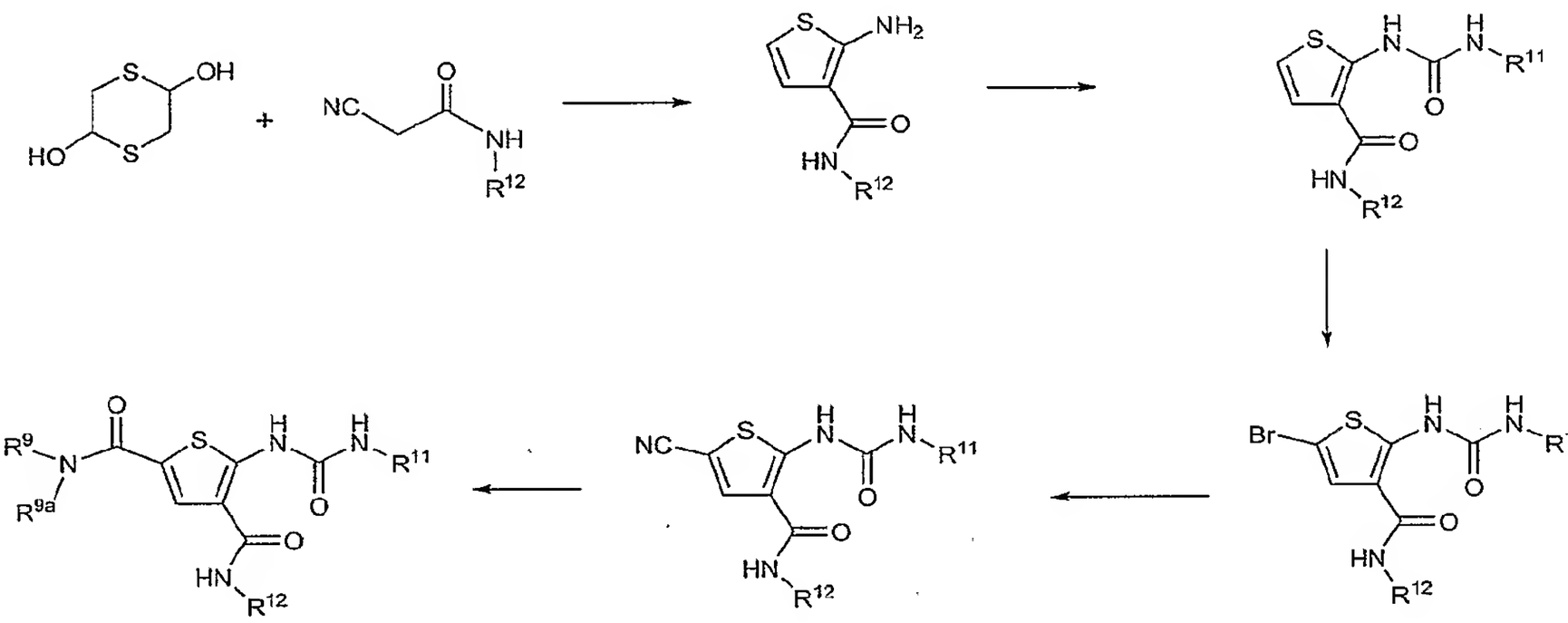
Synthesis of 2-ureido-3-carboxamido thiophene-5-carboxamides via nitriles



[00346] Condensation of 2,5-dihydroxy-1,4-dithiane with an appropriate cyanoacetamide gives the 2-aminothiophene-3-carboxamide. Conversion to the 2-ureido-3-carboxamidothiophene is achieved by the standard methods for urea formation, such as the use of sodium cyanate in acetic acid. Bromination with bromine in acetic acid produces the desired 5-bromo derivative. Cyanation is achieved using zinc cyanide with a transition metal catalyst such as a palladium compound, for example, tris(dibenzylideneacetone) dipalladium, in a DMF-benzonitrile solvent system with an added ligand such as 1,1'-bis(diphenylphosphino)ferrocene, preferentially at temperatures above room temperature. The obtained 2-ureido-3-carboxamido-5-cyanothiophene can be treated with dry HCl in methanol to give an imidate ester, which can be further transformed into the methyl ester. This ester is hydrolyzed by conventional methods, as, for example, by saponification, giving, in this instance, a carboxylate salt, which can be isolated, or directly transformed into the carboxylic acid by treatment with acid. This 2-ureido-3-carboxamido-thiophene-5-carboxylic acid can be coupled with amines using certain coupling agents such as HBTU tetrafluoroborate to produce 2-ureido-3-carboxamido-5-carboxamidothiophenes. Heating may be necessary depending on the type of amine being coupled, as in the case of certain anilines.

Scheme IIID

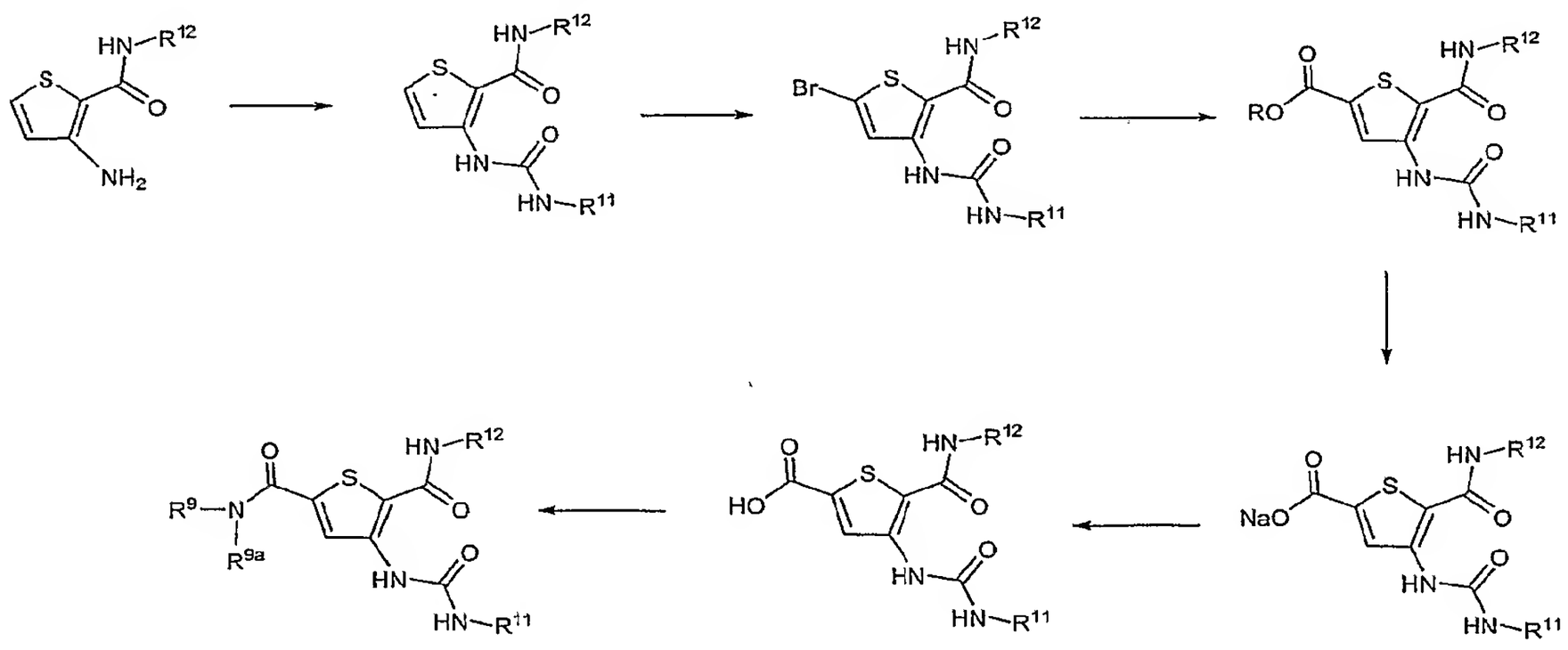
Synthesis of 2-ureido-3-carboxamido thiophene-5-carboxamides via nitriles



[00347] Condensation of 2,5-dihydroxy-1,4-dithiane with an appropriate cyanoacetamide gives the 2-aminothiophene-3-carboxamide. Conversion to the 2-ureido-3-carboxamidothiophene is achieved by the standard methods for urea formation, such as the use of sodium cyanate in acetic acid. Bromination with bromine in acetic acid produces the desired 5-bromo derivative. Cyanation is achieved using zinc cyanide with a transition metal catalyst such as a palladium compound, for example, tris(dibenzylideneacetone) dipalladium, in a DMF-benzonitrile solvent system with an added ligand such as 1,1'-bis(diphenylphosphino)ferrocene, preferentially at temperatures above room temperature. The obtained 2-ureido-3-carboxamido-5-cyanothiophene can be treated with dry HCl in an appropriate solvent and further treated with amines to produce 2-ureido-3-carboxamido-5-carboxamidothiophenes.

Scheme IVA

Synthesis of 2-carboxamido-3-ureido thiophene-5-amides from esters via carbonylation



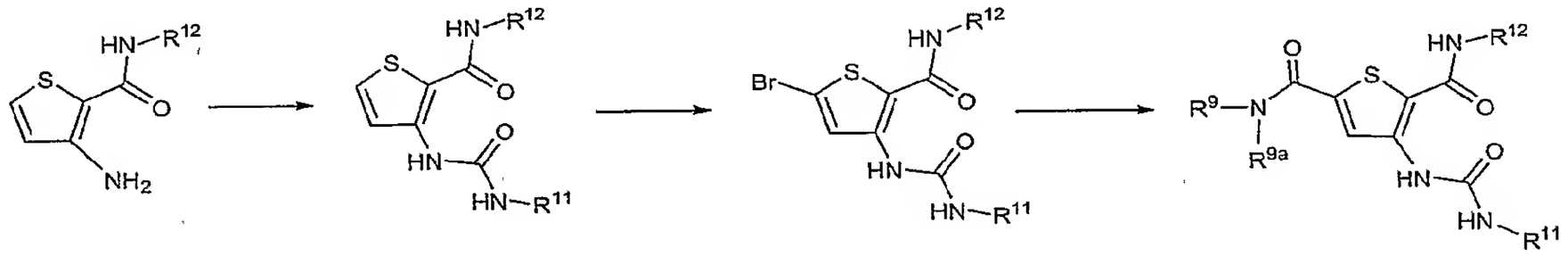
15

[00348] Starting from commercially available 2-carboxamido-3-aminothiophene, the 2-carboxamido-3-ureidothiophene is prepared via conventional procedures for urea formation such as reaction with sodium cyanate in acetic acid. Bromination using standard conditions may produce a mixture

of isomers, from which the desired 5-bromo derivative can be separated. Carbonylation of the 5-bromo derivative using carbon monoxide, with a transition metal catalyst, such as a palladium compound, for example palladium (II) acetate, optionally in the presence of an added ligand, for example, a phosphine, such as 1,1'-bis(diphenylphosphino)ferrocene in an alcohol, such as methanol, as solvent gives an ester, such as methyl 2-ureido-3-carboxamido-thiophene-5-carboxylate. This ester is hydrolyzed by conventional methods, as, for example, by saponification, giving, in this instance, a carboxylate salt, which can be isolated, or directly transformed into the carboxylic acid by treatment with acid. This 2-ureido-3-carboxamido-thiophene-5-carboxylic acid can be coupled with amines using certain coupling agents such as HBTU tetrafluoroborate to produce 2-carboxamido-3-ureido-5-carboxamidothiophenes. Heating may be necessary depending on the type of amine being coupled, as in the case of certain anilines.

Scheme IVB

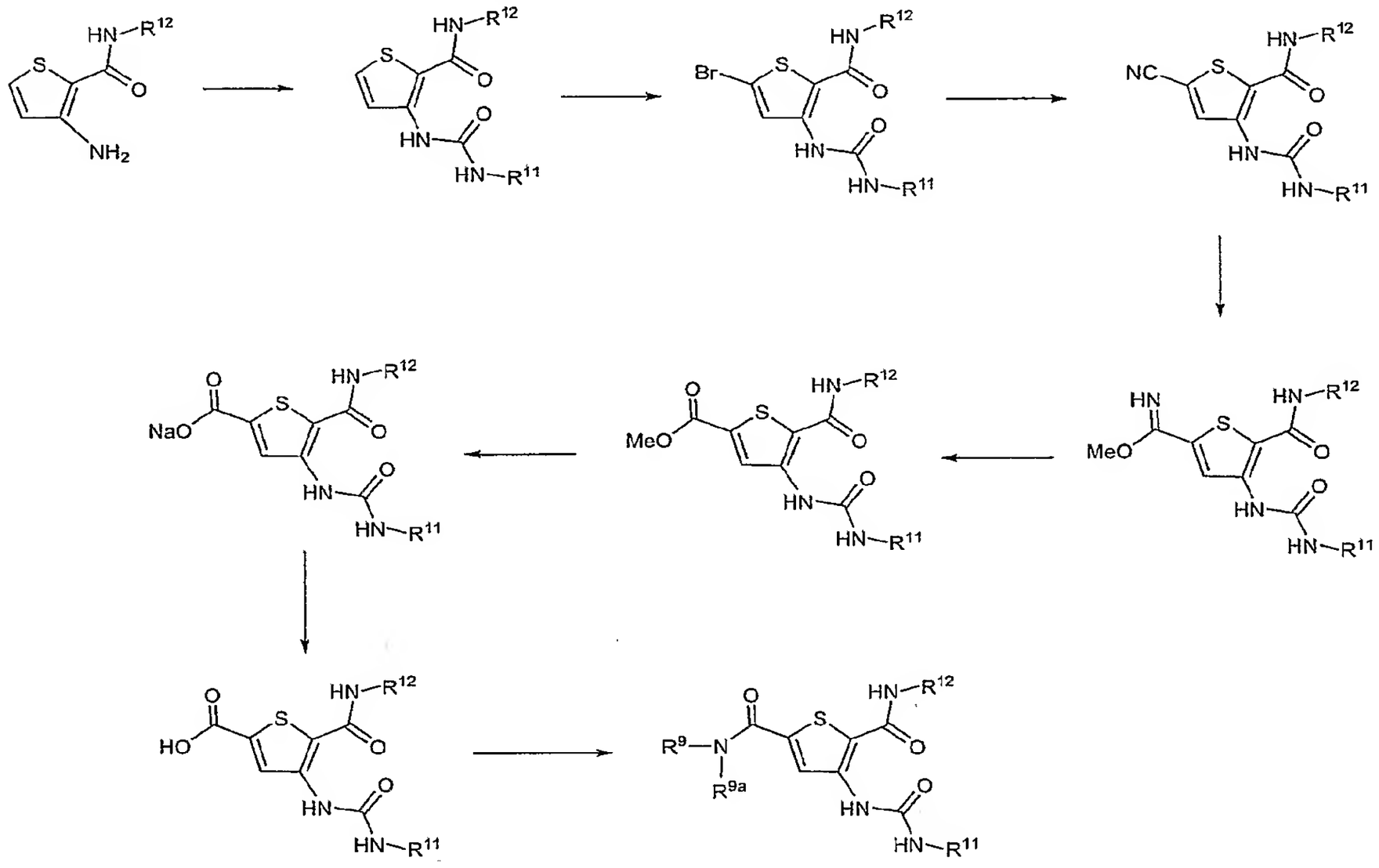
Synthesis of 2-carboxamido-3-ureido thiophene-5-amides via direct carbonylation to amides



[00349] Starting from commercially available 2-carboxamido-3-aminothiophene, the 2-carboxamido-3-ureidothiophene is prepared via conventional procedures for urea formation such as reaction with sodium cyanate in acetic acid. Bromination using standard conditions may produce a mixture of isomers, from which the desired 5-bromo derivative can be separated. Carbonylation of the 5-bromo derivative using carbon monoxide, with a transition metal catalyst, such as a palladium compound, for example palladium (II) acetate, optionally in the presence of an added ligand, for example, a phosphine, such as 1,1'-bis(diphenylphosphino)ferrocene in an appropriate solvent, such as DMF, containing the desired amine and a tertiary amine, gives an amide such as 2-carboxamido-3-ureido-5-carboxamidothiophene.

Scheme IVC

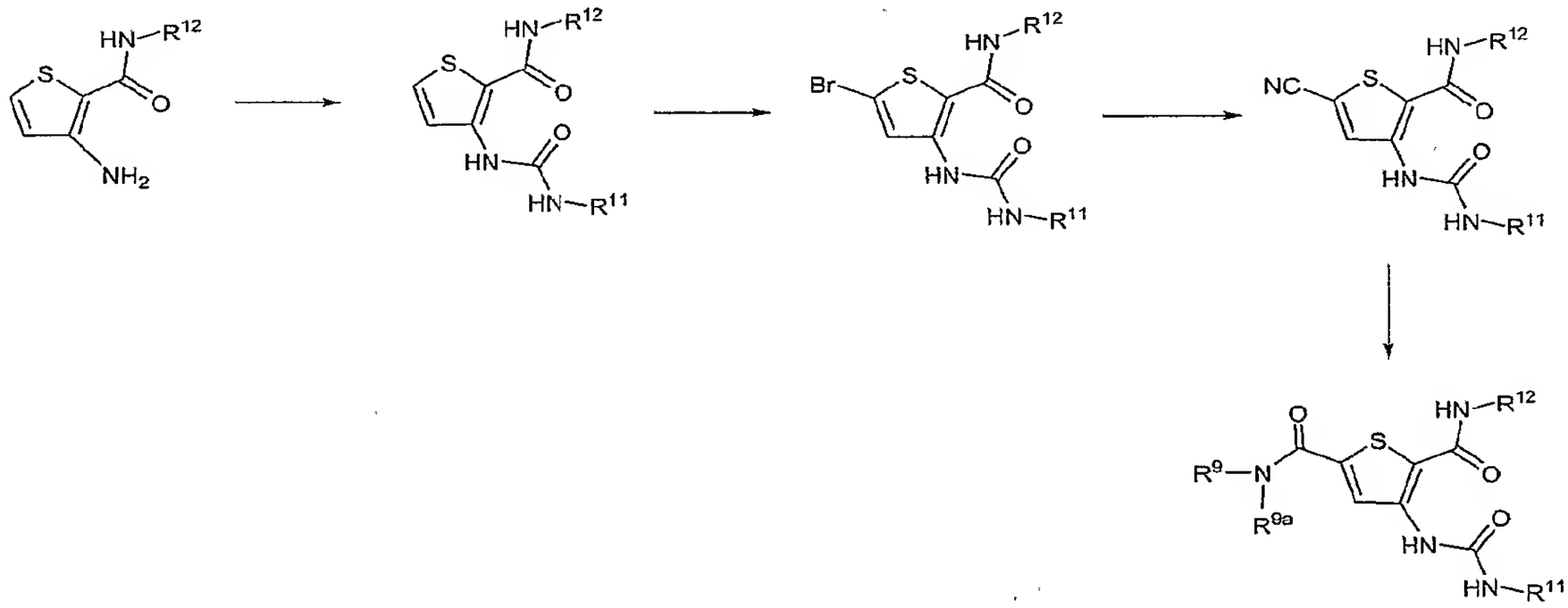
Synthesis of 2-carboxamido-3-ureido thiophene-5-amides from nitriles



[00350] Starting from commercially available 2-carboxamido-3-aminothiophene, the 2-carboxamido-3-ureidothiophene is prepared via conventional procedures for urea formation such as reaction with sodium cyanate in acetic acid. Bromination using standard conditions may produce a mixture of isomers, from which the desired 5-bromo derivative can be separated. Cyanation is achieved using zinc cyanide with a transition metal catalyst such as a palladium compound, for example, tris(dibenzylideneacetone) dipalladium, in a DMF-benzonitrile solvent system with an added ligand such as 1,1'-bis(diphenylphosphino)ferrocene, preferentially at temperatures above room temperature. The obtained 2-ureido-3-carboxamido-5-cyanothiophene can be treated with dry HCl in methanol to give an imidate ester, which can be further transformed into the methyl ester. This ester is hydrolyzed by conventional methods, as, for example, by saponification, giving, in this instance, a carboxylate salt, which can be isolated, or directly transformed into the carboxylic acid by treatment with acid. This 2-ureido-3-carboxamido-thiophene-5-carboxylic acid can be coupled with amines using certain coupling agents such as HBTU tetrafluoroborate to produce 2-ureido-3-carboxamido-5-carboxamidothiophenes. Heating may be necessary depending on the type of amine being coupled, as in the case of certain anilines.

Scheme IVD

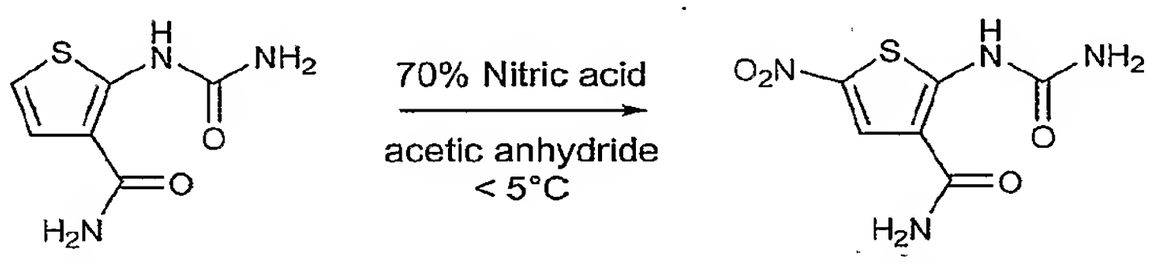
Synthesis of 2-carboxamido-3-ureido thiophene-5-amides from nitriles



[00351] Starting from commercially available 2-carboxamido-3-aminothiophene, the 2-carboxamido-3-ureidothiophene is prepared via conventional procedures for urea formation such as reaction with sodium cyanate in acetic acid. Bromination using standard conditions may produce a mixture of isomers, from which the desired 5-bromo derivative can be separated. Cyanation is achieved using zinc cyanide with a transition metal catalyst such as a palladium compound, for example, tris(dibenzylideneacetone) dipalladium, in a DMF-benzonitrile solvent system with an added ligand such as 1,1'-bis(diphenylphosphino)ferrocene, preferentially at temperatures above room temperature. The obtained 2-ureido-3-carboxamido-5-cyanothiophene can be treated with dry HCl in an appropriate solvent and further treated with amines to produce 2-ureido-3-carboxamido-5-carboxamidothiophenes.

EXAMPLES

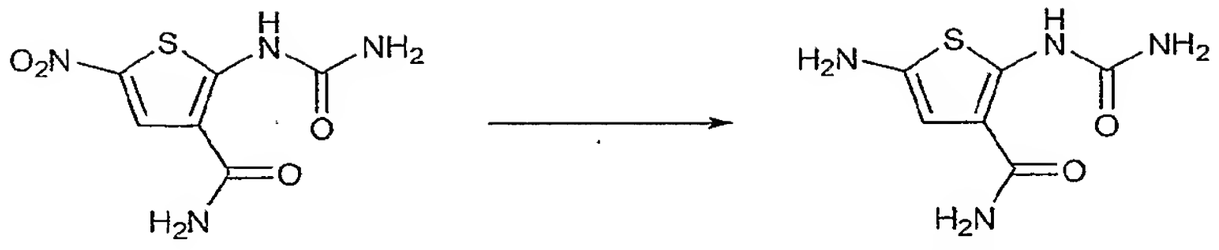
[00352] Example 1: Preparation of 2-[(aminocarbonyl)amino]-5-nitrothiophene-3-carboxamide



[00353]

[00354] 2-[(aminocarbonyl)amino]thiophene-3-carboxamide (3.00 g, 16.2 mmol) and acetic anhydride (112 mL) were combined and placed in an ice/water/acetone bath and cooled to 0°C. Separately, acetic anhydride (22 mL) and 70% nitric acid (3.8 mL) were combined at 0°C and the solution was added with vigorous stirring to the reaction mixture over 13 minutes, keeping the temperature between –1°C and 2°C. After 15 minutes, ice water (100 mL) was slowly added keeping the temperature below 12°C. After an additional half hour, more ice water (50 mL) was added and the mixture filtered cold, keeping the filtrate cold in an ice bath during filtration. The solid product was washed twice with 10 mL portions of water and dried under vacuum. The title compound is a brown solid. ^{1}H NMR (d_6-DMSO): δ 6.77-8.40 (2s + br s, 4H), 8.54 (s, 1H), 11.56 (s, 1H). ESI mass spectrum for $C_6H_7N_4O_4S^+$: 231 (M + 1).

[00355] Example 2A: Preparation of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide

[00356] 

[00357] 2-[(aminocarbonyl)amino]-5-nitrothiophene-3-carboxamide from Example 1 (0.189 g, 0.821 mmol) and concentrated HCl (1.8 mL, 22 mmol) were combined and placed in a water bath at 21°C. Then tin powder (0.202 g, 1.70 mmol) was slowly added. After 2.5 hours the mixture was filtered, the solid washed twice with the filtrate, followed by 10 mL of methanol and 30 mL of diethyl ether. ESI mass spectrum for $C_6H_9N_4O_2S^+$: 201 (M + 1). Anal. Calc'd. for $C_{12}H_{18}Cl_6N_8O_4S_2Sn(H_2O)_{1.3}$: C, 19.03; H, 2.74; Cl, 28.09, N, 14.80. Found: C, 19.27; H, 2.33; Cl, 27.75, N, 14.73.

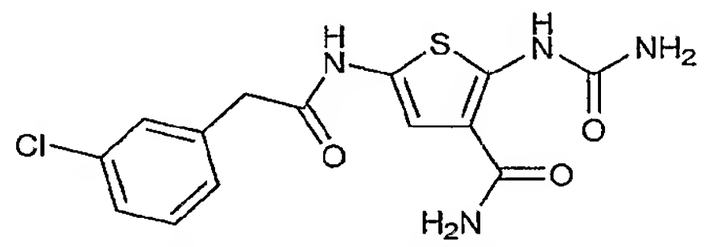
[00358] Example 2B: Preparation of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide

[00359] 2-[(aminocarbonyl)amino]-5-nitrothiophene-3-carboxamide from Example 1 (2.62 g, 11.4 mmol) and concentrated HCl (25.0 mL, 299 mmol) were combined and placed in a water bath at 21°C. Then tin powder (2.70 g, 22.7 mmol) was slowly added over 2.0 hours keeping the temperature below 30°C. After 30 min. the mixture was filtered, the solid washed twice with 6 mL portions of concentrated HCl, followed by 6 mL diethyl ether. The solid was then dried under vacuum.

[00360] Example 2C: Preparation of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide

[00361] 2-[(aminocarbonyl)amino]-5-nitrothiophene-3-carboxamide from Example 1 (2.62 g, 11.4 mmol) and concentrated HCl (25.0 mL, 299 mmol) were combined and placed in a water bath at 21°C. Then tin powder (2.70 g, 22.7 mmol) was slowly added over 2.0 hours keeping the temperature below 30°C. An additional 5 mL HCl was added to aid stirring. After 30 min. the mixture was filtered, and the solid was dried under vacuum.

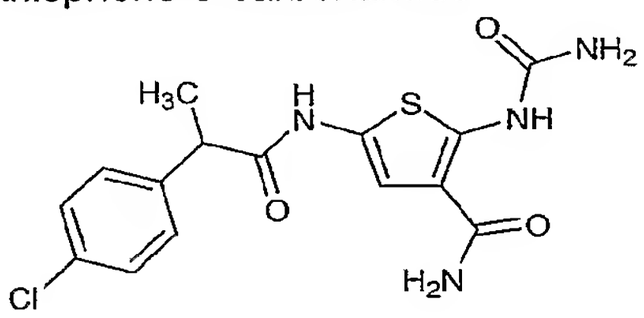
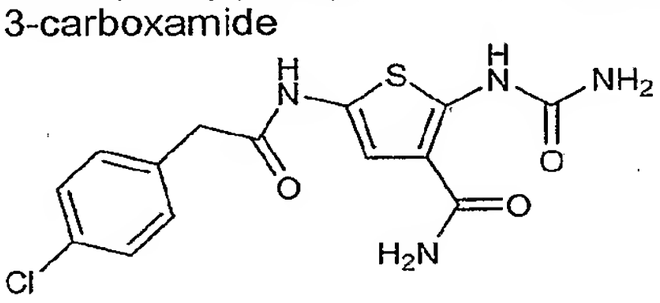
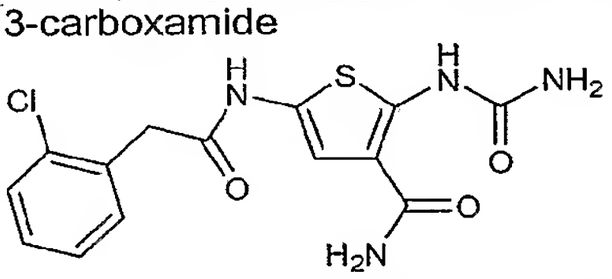
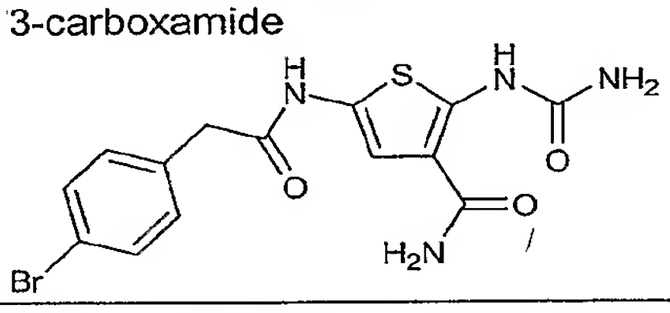
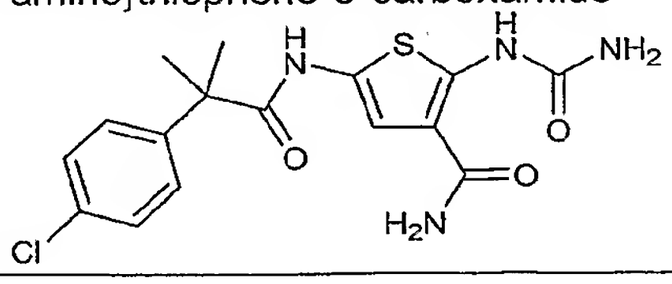
[00362] Example 3: 2-[(aminocarbonyl)amino]-5-{[(3-chlorophenyl)acetyl]amino}thiophene-3-carboxamide

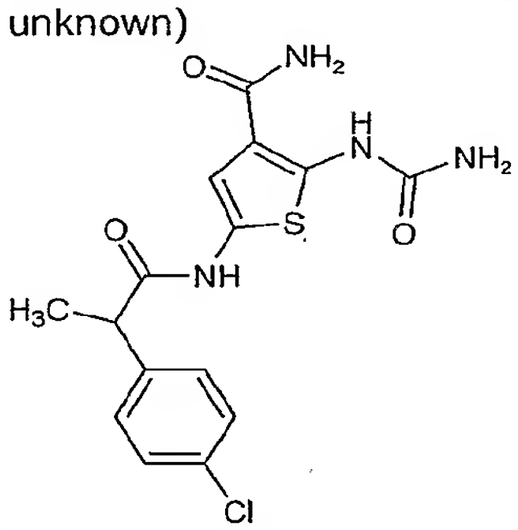
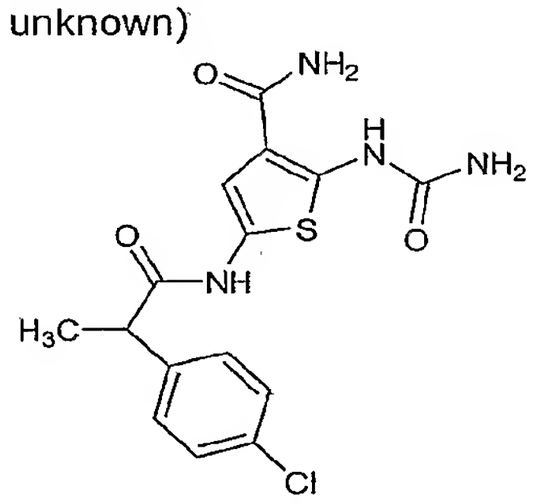
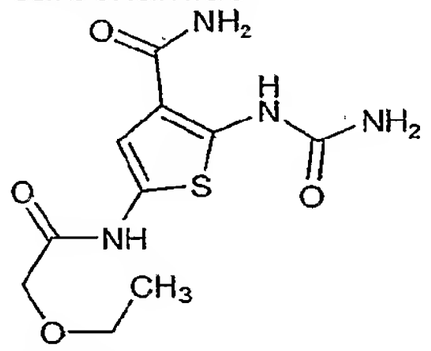
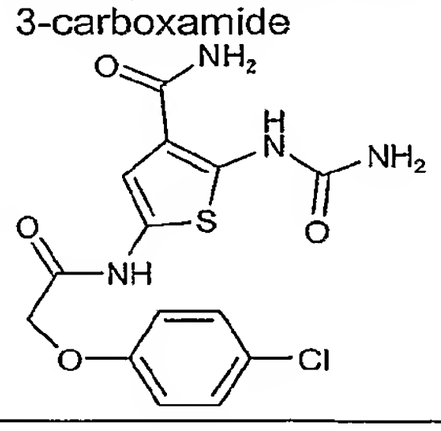
[00363] 

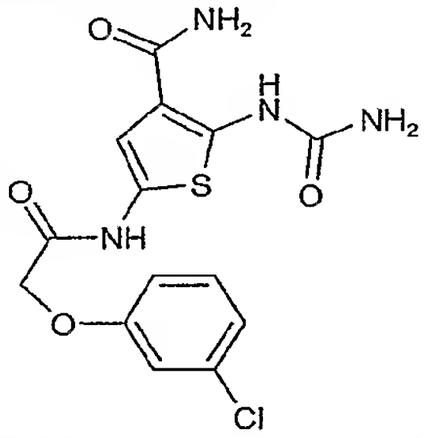
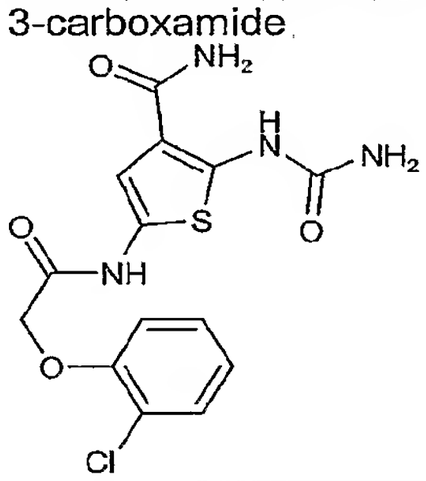
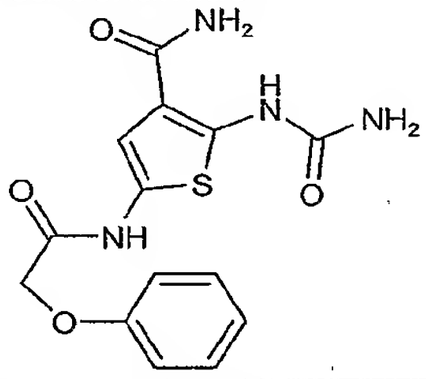
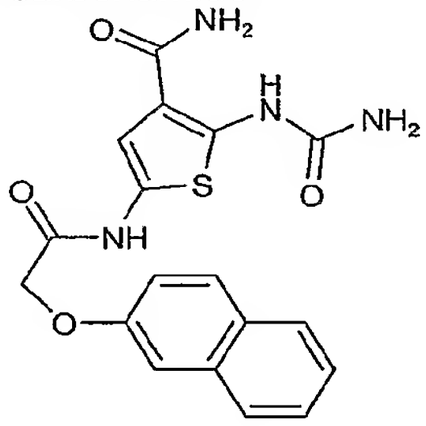
[00364] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.24 g) (prepared according to either Example 2A or Example 2B) was combined with 1 mmol of (3-chlorophenyl)acetic acid, HBTU (BF_4) (1 mmol), N,N-dimethylethylamine (1.0 mL, 9 mmol), and DMSO (1.0 mL). The mixture was stirred for 1 hour and most of liquids were stripped off. The residue was triturated in 100 mL CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with H_2O (100 mL) overnight, filtered, and washed with 20 mL ether. Then the product was dried under reduced pressure. ^1H NMR (CD_3OD): δ 3.66 (s, 2H), 6.83 (s, 1H), 7.20-7.38 (m, 3H), 7.37 (s, 1H). ESI mass spectrum for $C_{14}H_{14}ClN_4O_3S^+$: 353 (M + 1).

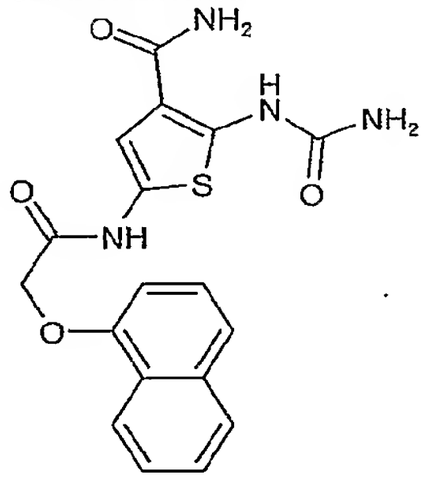
[00365] Examples 4-17, shown in Table V below, were prepared analogously to Example 3, substituting the appropriate carboxylic acid for the (3-chlorophenyl)acetic acid.

Table V

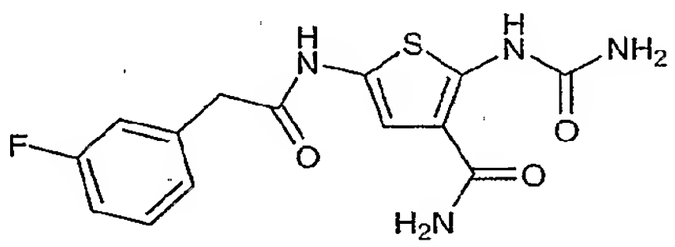
Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
4	2-[(aminocarbonyl) amino]-5-{[2-(4-chlorophenyl) propanoyl]amino} thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 1.38 (d, 3H, J = 7.05 Hz), 3.71 (q, 1H, J = 7.05 Hz), 6.65 (s, 1H), 7.20-7.37 (m, 4H).	367
5	2-[(aminocarbonyl) amino]-5-{[(4-chlorophenyl)acetyl] amino}thiophene-3-carboxamide 	(CD_3OD): δ 3.65 (s, 2H), 6.81 (s, 1H), 7.28-7.34 (m, 4H).	353
6	2-[(aminocarbonyl) amino]-5-{[(2-chlorophenyl)acetyl] amino}thiophene-3-carboxamide 	(CD_3OD): δ 3.84 (s, 2H), 6.84 (s, 1H), 7.24-7.33 (m, 2H), 7.34-7.44 (m, 2H).	353
7	2-[(aminocarbonyl) amino]-5-{[(4-bromophenyl)acetyl] amino}thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 3.35 (s, 2H), 6.69 (s, 1H), 7.13-7.22 (m, 2H), 7.35-7.43 (m, 2H).	397
8	2-[(aminocarbonyl) amino]-5-{[2-(4-chlorophenyl)-2-methylpropanoyl] amino}thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 1.48 (s, 6H), 6.59 (s, 1H), 7.25 (s, 4H).	381

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
9	2-[(aminocarbonyl) amino]-5-{[2-(4-chlorophenyl) propanoyl]amino}-thiophene-3-carboxamide ((-)-enantiomer, absolute configuration unknown) 	(CD_3OD/ d_6-DMSO (4:1)): δ 1.37 (d, 3H, J = 7.05 Hz), 3.70 (q, 1H, J = 7.05 Hz), 6.65 (s, 1H), 7.20–7.38 (m, 4H).	367
10	2-[(aminocarbonyl) amino]-5-{[2-(4-chlorophenyl) propanoyl]amino}-thiophene-3-carboxamide ((+)-enantiomer, absolute configuration unknown) 	(CD_3OD/ d_6-DMSO (4:1)): δ 1.39 (d, 3H, J = 7.05 Hz), 3.71 (q, 1H, J = 7.05 Hz), 6.66 (s, 1H), 7.19–7.37 (m, 4H).	367
11	2-[(aminocarbonyl) amino]-5-[(ethoxyacetyl)amino]thiophene-3-carboxamide 	(d_6-DMSO): δ 1.17 (t, 3H, J = 7.1 Hz), 3.53 (q, 1H, J = 7.1 Hz), 4.02 (s, 2H), 6.77 (br s, 2H), 6.84 (s, 1H), 7.13 (br s, 1H), 7.50 (br s, 1H), 10.49 (s, 1H), 10.90 (s, 1H).	287
12	2-[(aminocarbonyl) amino]-5-{[(4-chlorophenoxy)acetyl]amino}thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 4.60 (s, 2H), 6.79 (s, 1H), 6.94 (dm, 2H, J = 8.9 Hz), 7.22 (dm, 2H, J = 9.0 Hz).	369

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
13	2-[(aminocarbonyl) amino]-5-{[(3-chlorophenoxy)acetyl]amino}thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 4.65 (s, 2H), 6.84 (s, 1H), 6.88-7.07 (m, 3H), 7.30 (t, 2H, J = 8.1 Hz).	369
14	2-[(aminocarbonyl) amino]-5-{[(2-chlorophenoxy)acetyl]amino}thiophene-3-carboxamide 	(d_6-DMSO): δ 4.91 (s, 2H), 6.79 (br s, 2H), 6.86 (s, 1H), 6.97 (t, 1H, J = 7.6 Hz), 7.05 (d, 1H,J = 7.7 Hz), 7.15 (br s, 1H), 7.28 (t, 1H, J = 8.6 Hz), 7.44 (d, 1H, J = 7.4 Hz), 7.57 (br s, 1H), 10.85 (s, 1H), 10.91 (s, 1H).	369
15	2-[(aminocarbonyl) amino]-5-[(phenoxyacetyl) amino]thiophene-3-carboxamide 	(d_6-DMSO): δ 4.50 (s, 2H), 6.75 (br s, 2H), 6.87 (s, 1H), 6.92-7.01 (m, 3H), 7.14 (br s, 1H), 7.30 (t, 2H, J = 7.9 Hz), 7.47 (br s, 1H), 10.82 (s, 1H), 10.91 (s, 1H).	335
16	2-[(aminocarbonyl) amino]-5-{[(2-naphthyloxy)acetyl] amino}thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 4.76 (s, 2H), 6.81 (s, 1H), 7.20-7.45 (m, 4H), 7.61-7.82 (m, 3H).	385

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
17	2-[(aminocarbonyl) amino]-5-{[(1-naphthyloxy)acetyl] amino}thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 4.84 (s, 2H), 6.82 (s, 1H), 6.85 (d, 1H, J = 7.5 Hz), 7.32 (t, 2H, J = 8.0 Hz), 7.38-7.50 (m, 3H), 7.70-7.80 (m, 1H), 8.26-8.34 (m, 1H).	385

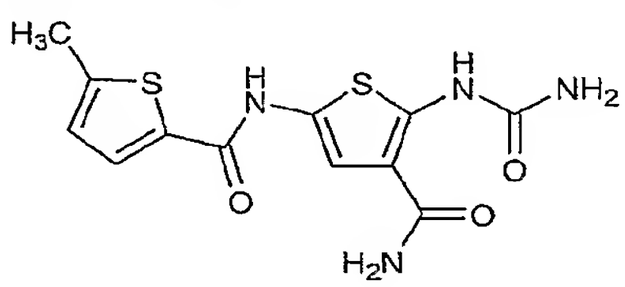
[00366] Example 18: 2-[(aminocarbonyl)amino]-5-{[(3-fluorophenyl)acetyl]amino}thiophene-3-carboxamide



[00367]

[00368] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.24 g) (prepared according to either Example 2A or Example 2B) was combined with 1 mmol of (3-fluorophenyl)acetic acid, HBTU (BF_4) (1 mmol), N,N-dimethylethylamine (1.0 mL, 9 mmol), and DMSO (1.0 mL). The mixture was stirred for 1 hour and most of liquids were stripped off. The residue was triturated in 50 mL H_2O for 3 hours. The slurry was filtered, triturated with K_2CO_3 solution (0.15 g K_2CO_3 in 50 mL H_2O) overnight, filtered, and washed with H_2O and ether. The product was dried under reduced pressure. ^{1}H NMR (CD_3OD): δ 3.30 (s, 2H), 6.83 (s, 1H), 6.95 (t, 1H, J = 7.88 Hz), 7.08 (d, 1H, J = 9.74 Hz), 7.14 (d, 1H, J = 7.55 Hz), 7.23 (d,d, 1H, J = 7.55 Hz, J = 6.55 Hz). ESI mass spectrum for $C_{14}H_{14}FN_4O_3S^+$: 337 (M + 1).

[00369] Example 19: N-{4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}-5-methylthiophene-2-carboxamide

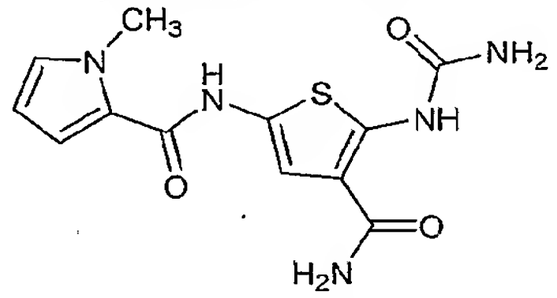
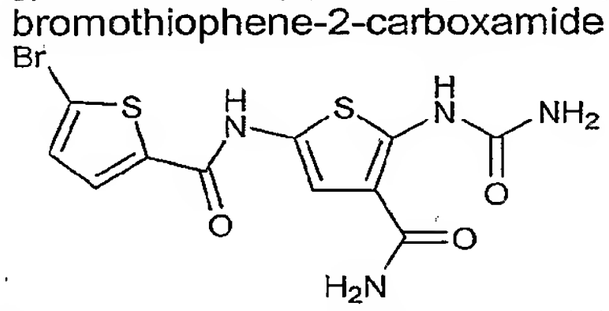
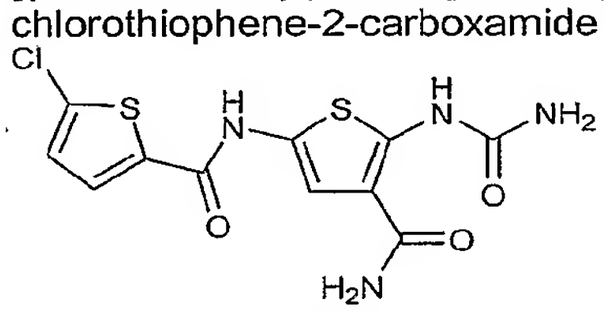
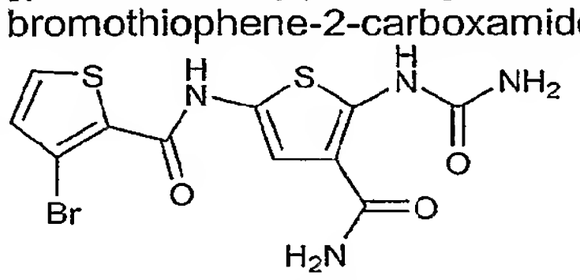
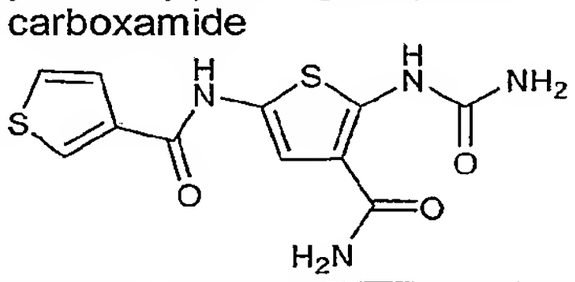


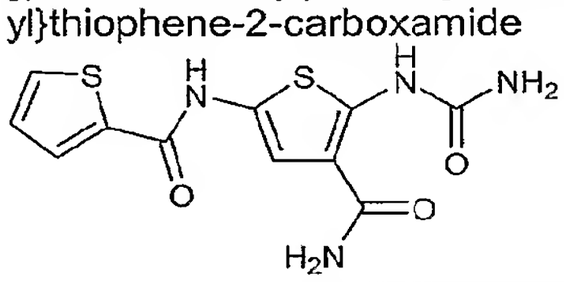
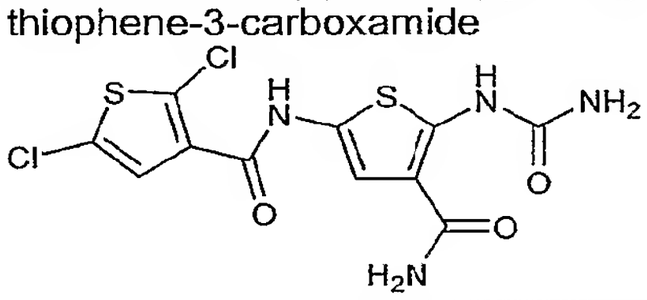
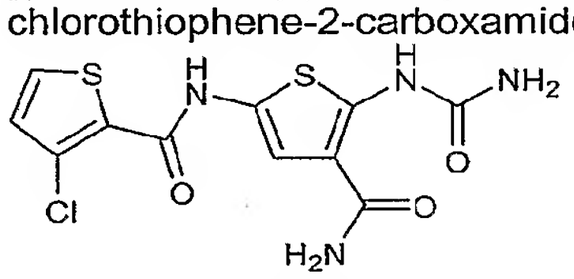
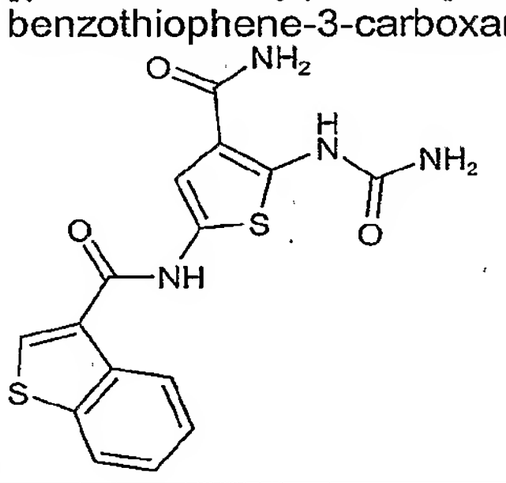
[00370]

[00371] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.24 g) (prepared according to either Example 2A or Example 2B) was combined with 1 mmol of 5-methylthiophene-2-carboxylic acid, HBTU (BF_4) (1 mmol), N,N-dimethylethylamine (1.0 mL, 9 mmol), and DMSO (1.0 mL). The mixture was stirred for 1 hour, then most of the liquids were stripped off. The residue was triturated in 100 mL CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with H_2O (100 mL) overnight, filtered, washed with 20 mL ether, and triturated with 2 mL CH_3OH for 30 minutes. The product was filtered and dried under reduced pressure. ^{1}H NMR (CD_3OD): δ 2.57 (s, 3H), 6.85 (d, 1H, J = 3 Hz), 6.93 (s, 1H), 7.64 (d, 1H, J = 3 Hz). ESI mass spectrum for $C_{12}H_{13}N_4O_3S_2^+$: 325 (M + 1).

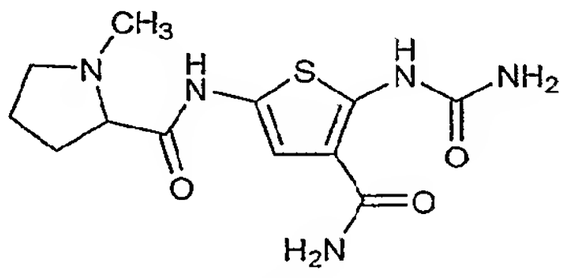
[00372] Examples 20-28, shown in Table VI below, were prepared analogously to Example 19, substituting the appropriate carboxylic acid for the 5-methylthiophene-2-carboxylic acid.

Table VI

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
20	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}-1-methyl-1H-pyrrole-2-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 3.84 (s, 3H), 6.04-6.09 (m, 1H), 6.83 (s, 1H), 6.95-7.01 (m, 2H).	308
21	N-{4-(aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl}-5-bromothiophene-2-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 6.99 (s, 1H), 7.24 (d, 1H, J = 4.03 Hz), 7.69 (d, 1H, J = 4.02 Hz).	389
22	N-{4-(aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl}-5-chlorothiophene-2-carboxamide 	(CD_3OD): 6.88 (s, 1H), 7.08 (d, 1H, J = 4 Hz), 7.67 (d, 1H, J = 4 Hz).	345
23	N-{4-(aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl}-3-bromothiophene-2-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 7.01 (s, 1H), 7.22 (d, 1H, J = 5.24 Hz), 7.79 (d, 1H, J = 5.24 Hz).	389
24	2-[(Aminocarbonyl) amino]-5-[(thien-3-ylcarbonyl)amino] thiophene-3-carboxamide 	(CD_3OD): 6.94 (s, 1H), 7.53 (dd 1H, J = 5.1, 2.9 Hz), 7.60 (dd 1H, J = 5.1 Hz, 1.2 Hz), 8.19 (dd 1H, J = 2.9, 1.2 Hz).	311

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
25	N-{4-(aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl}thiophene-2-carboxamide 	(CD_3OD): 6.99 (s, 1H), 7.22 (dd 1H, J = 3.8, 0.9 Hz), 7.76 (d 1H, J = 5.04 Hz), 7.87 (d 1H, J = 4.92 Hz).	311
26	2-[(aminocarbonyl) amino]-5-{[(2,5-dichlorothien-3-yl) carbonyl]amino} thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 6.98 (s, 1H), 7.36 (s, 1H).	379
27	N-{4-(Aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl}-3-chlorothiophene-2-carboxamide 	(CD_3OD): δ 6.97 (s, 1H), 7.09 (d, 1H, J = 5.3 Hz), 7.73 (d, 1H, J = 5.2 Hz).	345
28	N-{4-(aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl}-1-benzothiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 6.83 (s, 1H), 7.28-7.42 (m, 2H), 7.88 (d, 1H, J = 7.05 Hz), 8.25 (s, 1H), 8.36 (d, 1H, J = 7.04 Hz), 10.86 (s, 1H).	361

[00373] Example 29: N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}-1-methylprolinamide



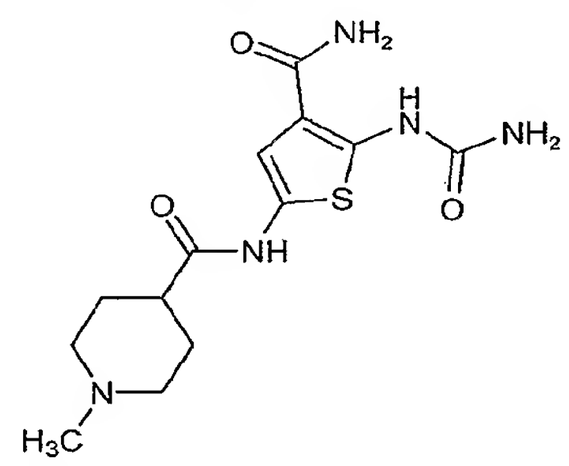
[00374]

[00375] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.1 g) (prepared according to either Example 2A or Example 2B) was combined with 0.4 mmol of an amino acid, PS-carbodiimide (1 g), PS-diethylenetriamine (2.62 g), and DMF (10 mL). The mixture was stirred overnight, then filtered and the solid was washed with DMF. The DMF was stripped off, and the residue was washed with CH_2Cl_2, dried, and extracted with CH_3OH (50 mL x 2). After removing methanol, the solid was triturated in 5 mL of a saturated solution of sodium bicarbonate for 3 hours. The slurry was filtered, and most of it was dissolved in CH_3OH and filtered again. The CH_3OH was removed, and the

product was dried under reduced pressure. ^{1}H NMR (CD_3OD): δ 1.80-1.96 (m, 3H), 2.18-2.30 (m, 1H), 2.34-2.46 (m, 4H), 2.96-3.04 (m, 1H), 3.14-3.22 (m, 1H), 6.95 (s, 1H). ESI mass spectrum for $C_{12}H_{18}N_5O_3S^+$: 312 (M + 1).

[00376] Example 30: N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}-1-methylpiperidine-4-carboxamide

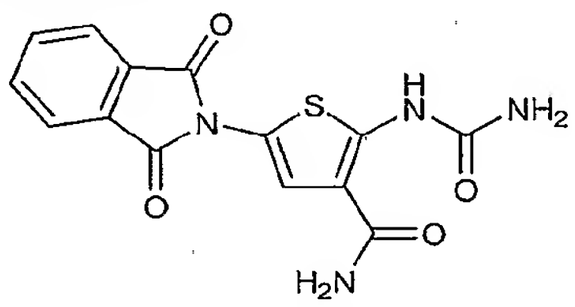
[00377]



[00378] Prepared analogously to Example 29. ^{1}H NMR (CD_3OD/d_6-DMSO (4:1)): δ 1.60-1.78 (m, 4H), 1.88-2.04 (m, 2H), 2.15 (s, 3H), 2.19-2.30 (m, 1H), 2.82 (dm, 2H, J = 11.8 Hz), 6.68 (s, 1H). Mass of the Molecular ion: 326 (M + 1).

[00379] Example 31A: 2-[(aminocarbonyl)amino]-5-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)thiophene-3-carboxamide

[00380]

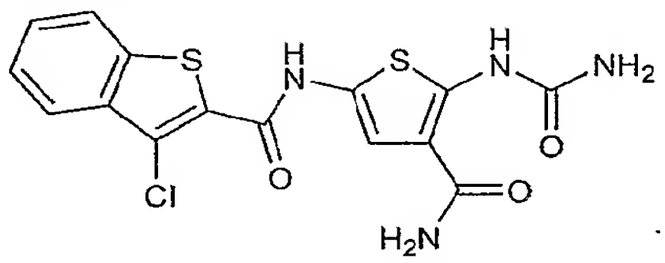


[00381] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.1 g) (prepared according to Example 2B) was combined with mono-methyl phthalate (0.311 g, 1.73 mmol), HBTU (BF_4) (0.554 g, 1.73 mmol), N,N-dimethylethylamine (1.3 mL, 12 mmol), and DMSO (1.7 mL). The mixture was stirred for two hours and then most of the DMSO was stripped off. The residue was then triturated in 100 mL H_2O, followed by continued trituration after the addition of anhydrous K_2CO_3 (0.71 g, 5.1 mmol) to the water. The slurry was then filtered, and the solid washed with 5 mL H_2O. The solid was then dissolved in 5 mL DMF, slowly added to 200 ml H_2O, then triturated overnight. The precipitate was then filtered and washed with 10 mL H_2O. The product was then dried under vacuum. ^{1}H NMR (d_6-DMSO): δ 6.96 (br s, 2H), 7.25 (br s, 1H), 7.43 (s, 1H), 7.70 (br s, 1H), 7.84-7.89 (m, 2H), 7.90-7.95 (m, 2H), 11.09 (s, 1H). HRMS $C_{14}H_{11}N_4O_4S^+$: theoretical: 331.0496; found: 331.0523 (M + 1).

[00382] Example 31B: 2-[(aminocarbonyl)amino]-5-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)thiophene-3-carboxamide

[00383] Made similarly to Example 31A, except on a 2.6 mmole scale, 2-cyanobenzoic acid (0.574 g, 3.9 mmol) was used in place of mono-methyl phthalate, stirring was for 3.5 hours, the residue was trituated in 45 mL H_2O, in 25 mL CH_3OH:CH_3CN (4:1), in 10 mL H_2O with 1.5 g anhydrous K_2CO_3, and then in 10 mL chloroform. The product was then dissolved in DMF, precipitated with CH_3CN, triturated in 10 mL H_2O, and dried under vacuum.

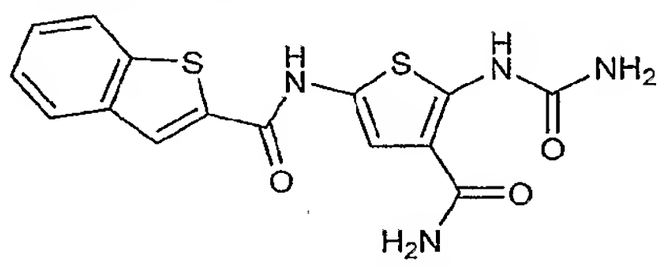
[00384] Example 32: N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}-3-chloro-1-benzothiophene-2-carboxamide



[00385]

[00386] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.1 g) (prepared according to Example 2C) was combined with 3-chlorobenzo[b]thiophene-2-carboxylic acid (0.364 g, 1.71 mmol), PS-carbodiimide resin (2.49 g, 3.44 mmol), PS-diethylenetriamine (6.51 g, 17.1 mmol), and DMF (45.0 mL). The mixture was stirred overnight, filtered, and washed with 45 mL DMF. The DMF was stripped from the filtrate/wash and the residue triturated in 100 mL H_2O, followed by sonication in 10 mL CH_3OH and drying under vacuum. ^1H NMR (d_6-DMSO): δ 6.84 (br s, 2H), 7.04 (s, 1H), 7.17 (br s, 1H), 7.61 (br s, 3H), 7.92 (br s, 1H), 8.14 (br s, 1H), 10.89 (s, 1H), 11.33 (s, 1H).

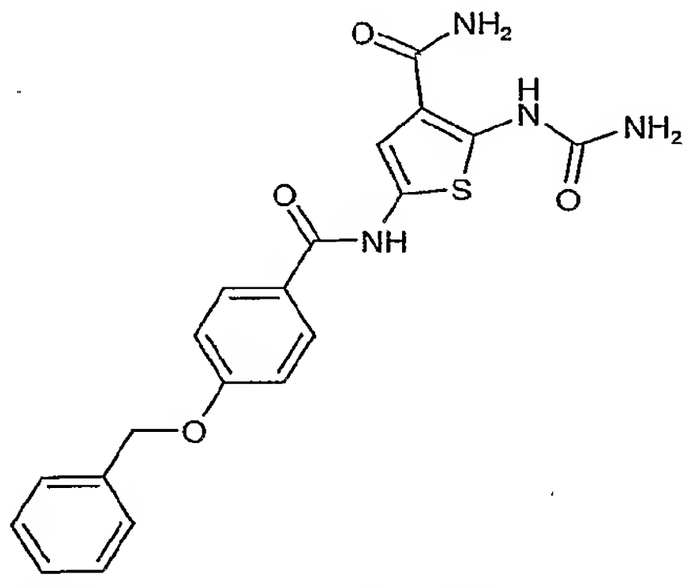
[00387] Example 33: N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}-1-benzothiophene-2-carboxamide



[00388]

[00389] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.1 g) (prepared according to Example 2C) was combined with benzo[b]thiophene-2-carboxylic acid (0.305 g, 1.71 mmol), HATU (0.652 g, 1.71 mmol), DMF (10 mL) and triethylamine (1.6 mL, 11.5 mmol). The mixture was then stirred overnight and the DMF stripped off. The residue was then triturated in 120 mL H_2O, triturated and sonicated in 50 mL 20:80 CH_3OH:H_2O, sonicated in 25 mL CH_3OH three times, and then dried under vacuum. ^1H NMR (d_6-DMSO): δ 6.82 (br s, 2H), 7.00 (s, 1H), 7.17 (br s, 1H), 7.41-7.50 (m, 2H), 7.63 (br s, 1H), 7.96-8.07 (m, 2H), 8.30 (s, 1H), 10.88 (s, 1H), 11.45 (s, 1H). ESI mass spectrum for $C_{15}H_{13}N_4O_3S_2^+$: 361 (M + 1).

[00390] Example 34: 2-[(Aminocarbonyl)amino]-5-{[4-(benzyloxy)benzoyl]amino}thiophene-3-carboxamide



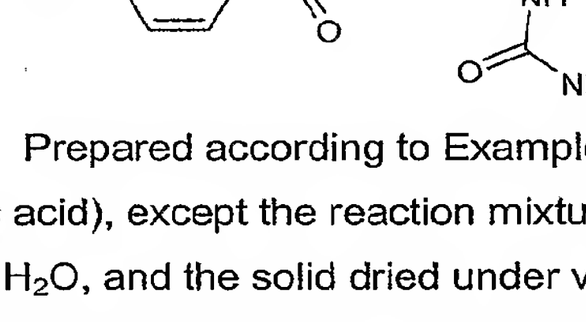
[00391]

[00392] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (prepared according to Example 2A) was combined with 4-benzyloxybenzoic acid (0.293 g, 1.28 mmol),

HATU (0.493 g, 1.30 mmol), triethylamine (1.2 mL, 8.6 mmol), and DMF (5.0 mL). The mixture was stirred overnight, and then added to H_2O (50 mL). The precipitate was filtered, washed with H_2O, triturated in H_2O, and then dried under vacuum. The title compound is a gray solid. ^1H NMR (d_6-DMSO): δ 5.17 (s, 2H), 6.77 (br s, 2H), 6.91 (s, 1H), 7.04-7.22 (d + br s, 3H), 7.27-7.62 (m, 6H), 7.92 (d, 2H, J = 8.7 Hz), 10.82 (s, 1H), 11.97 (s, 1H). ESI mass spectrum for $C_{20}H_{19}N_4O_4S^+$: 411 (M + 1).

[00393] Example 35: 2-[(Aminocarbonyl)amino]-5-[(3-cyanobenzoyl)amino]thiophene-3-carboxamide

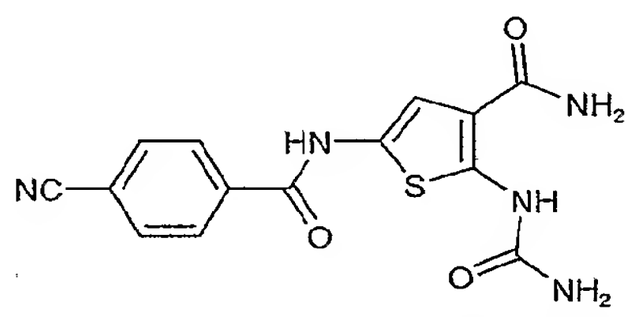
[00394]



[00395] Prepared according to Example 34 (substituting 3-cyanobenzoic acid for the 4-benzyloxybenzoic acid), except the reaction mixture was filtered, the solid washed with H_2O and then triturated in H_2O, and the solid dried under vacuum. The title compound is a light brown solid. ^1H NMR (d_6-DMSO): δ 6.80 (br s, 2H), 6.98 (s, 1H), 7.16 (br s, 1H), 7.61 (br s, 1H), 7.73 (t, 1H, J = 7.8 Hz), 8.03 (d, 1H, J = 7.7 Hz), 8.22 (d, 1H, J = 8.1 Hz), 8.37 (s, 1H), 10.87 (s, 1H), 11.33 (s, 1H). ESI mass spectrum for $C_{14}H_{12}N_5O_3S^+$: 330 (M + 1).

[00396] Example 36: 2-[(Aminocarbonyl)amino]-5-[(4-cyanobenzoyl)amino]thiophene-3-carboxamide

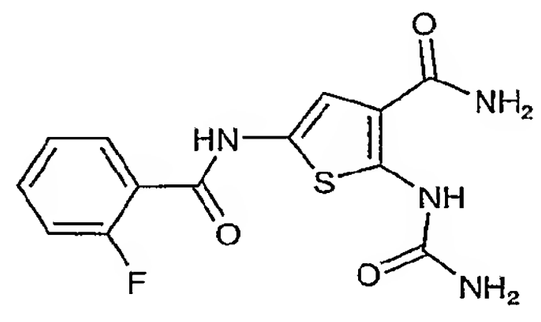
[00397]



[00398] Prepared according to Example 34 (substituting 4-cyanobenzoic acid for the 4-benzyloxybenzoic acid), except the reaction mixture was filtered, the solid washed with H_2O and then triturated twice in H_2O, and the solid dried under vacuum. The title compound is a brown solid. ^1H NMR (d_6-DMSO): δ 6.80 (br s, 2H), 6.99 (s, 1H), 7.16 (br s, 1H), 7.61 (br s, 1H), 7.99 (d, 2H, J = 8.6 Hz), 8.09 (d, 2H, J = 8.5 Hz), 10.86 (s, 1H), 11.41 (s, 1H). HRMS $C_{14}H_{12}N_5O_3S^+$: theoretical: 330.0655, found: 330.0644 (M + 1).

[00399] Example 37: 2-[(Aminocarbonyl)amino]-5-[(2-fluorobenzoyl)amino]thiophene-3-carboxamide

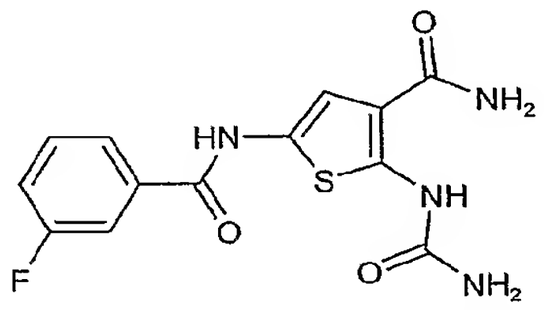
[00400]



[00401] Prepared according to Example 34 (substituting 2-fluorobenzoic acid for the 4-benzyloxybenzoic acid), except 20 mL DMF was used, and the reaction mixture was filtered. The filtrate

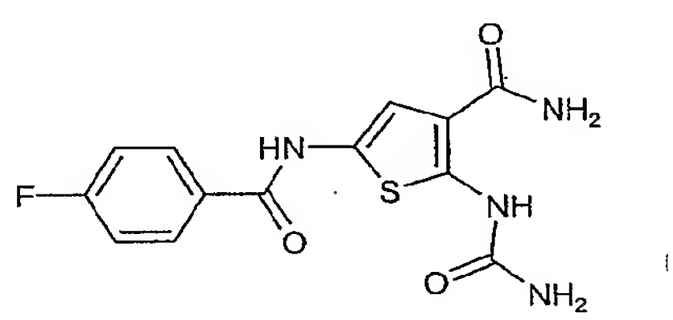
was then stripped of DMF, the residue triturated in H_2O, then triturated in CH_3OH, and dried under vacuum. The title compound is a brown solid. ^1H NMR (d_6-DMSO): δ 6.79 (br s, 2H), 6.90 (s, 1H), 7.13 (br s, 1H), 7.27-7.35 (m, 2H), 7.51-7.66 (m, 3H), 10.85 (s, 1H), 11.18 (s, 1H). ESI mass spectrum for $C_{13}H_{12}FN_4O_3S^+$: 323 (M + 1).

[00402] Example 38: 2-[(Aminocarbonyl)amino]-5-[(3-fluorobenzoyl)amino]thiophene-3-carboxamide

[00403] 

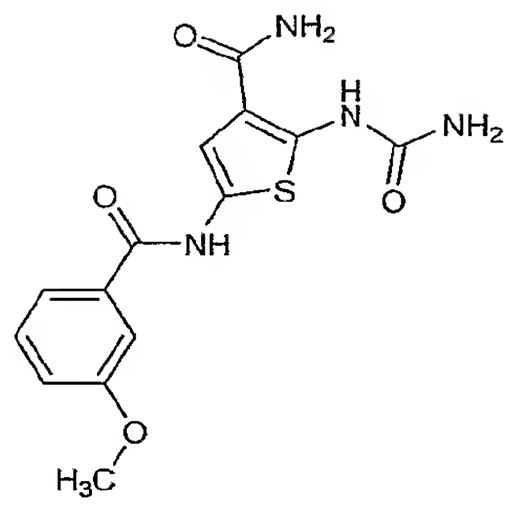
[00404] Prepared according to Example 34 (substituting 3-fluorobenzoic acid for the 4-benzyloxybenzoic acid), except 20 mL DMF was used, and the reaction mixture was filtered. The filtrate was then stripped of DMF, the residue triturated twice in H_2O, then triturated in CH_3OH, and dried under vacuum. The title compound is a brown solid. ^1H NMR (d_6-DMSO): δ 6.79 (br s, 2H), 6.97 (s, 1H), 7.14 (br s, 1H), 7.39-7.45 (m, 1H), 7.51-7.65 (m + br s, 2H), 7.72-7.82 (m, 2H), 10.85 (s, 1H), 11.21 (s, 1H). ESI mass spectrum for $C_{13}H_{12}FN_4O_3S^+$: 323 (M + 1).

[00405] Example 39: 2-[(Aminocarbonyl)amino]-5-[(4-fluorobenzoyl)amino]thiophene-3-carboxamide

[00406] 

[00407] Prepared according to Example 34 (substituting 4-fluorobenzoic acid for the 4-benzyloxybenzoic acid), except 20 mL DMF was used, and the reaction mixture was filtered. The filtrate was then stripped of DMF, the residue triturated in H_2O, then triturated in CH_3OH, then triturated in 3 wt% aqueous K_2CO_3 solution followed by water washes, and then dried under vacuum. The title compound is a brown solid. ^1H NMR (d_6-DMSO): δ 6.78 (br s, 2H), 6.95 (s, 1H), 7.14 (br s, 1H), 7.30-7.39 (m, 2H), 7.57 (br s, 1H), 7.97-8.06 (m, 2H), 10.84 (s, 1H), 11.15 (s, 1H). ESI mass spectrum for $C_{13}H_{12}FN_4O_3S^+$: 323 (M + 1).

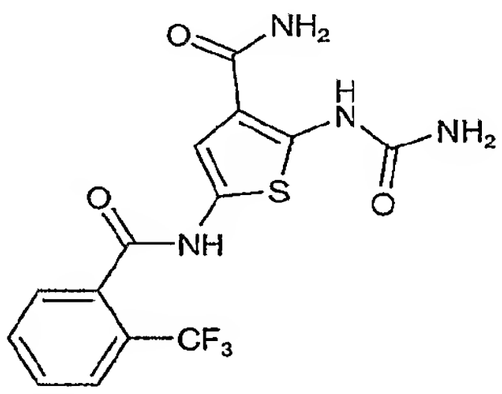
[00408] Example 40: 2-[(Aminocarbonyl)amino]-5-[(3-methoxybenzoyl)amino]thiophene-3-carboxamide



[00409]

[00410] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.293 g) (prepared according to Example 2B) was combined with m-anisic acid (0.264 g, 1.74 mmol), HBTU (BF_4) (0.553 g, 1.72 mmol), N,N-dimethylethylamine (1.3 mL, 12 mmol), and DMSO (1.7 mL). The mixture was stirred for two hours and then most of the DMSO was stripped off. The residue was then triturated in 100 mL H_2O, followed by continued trituration after the addition of anhydrous K_2CO_3 (0.71 g, 5.1 mmol) to the water. The slurry was then filtered, and the solid washed with 5 mL H_2O. The solid was then dissolved in 5 mL DMF, slowly added to 200 ml H_2O, then triturated overnight. The precipitate was then filtered and washed with 10 mL H_2O. The product was then dried under vacuum to afford a tan solid. ^1H NMR (d_6-DMSO): δ 3.80 (s, 3H), 6.78 (br s, 2H), 6.95 (s, 1H), 7.04-7.23 (m+br s, 2H), 7.41 (t, 1H, J = 7.9 Hz), 7.44-7.48 (m, 1H), 7.49-7.64 (m + br s, 2H), 10.83 (s, 1H), 11.08 (s, 1H). HRMS $C_{14}H_{15}N_4O_4S^+$: theoretical: 335.0809, found: 335.0833 (M+1).

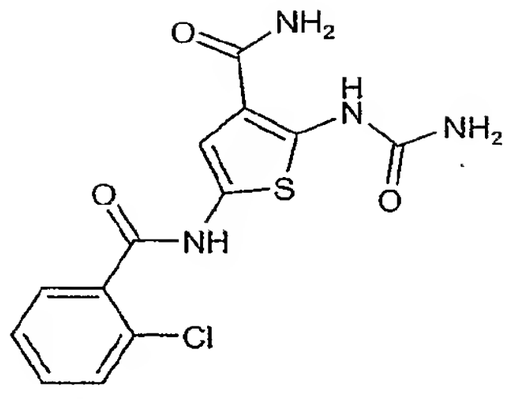
[00411] Example 41: 2-[(Aminocarbonyl)amino]-5-{[2-(trifluoromethyl)benzoyl]amino}thiophene-3-carboxamide



[00412]

[00413] Prepared according to Example 40 (substituting 2-trifluoromethylbenzoic acid for the m-anisic acid), except stirring was maintained for 3.5 hrs., and after the initial water trituration, the residue was then triturated in 13 wt% aqueous K_2CO_3 solution, $CDCl_3$, and finally diethyl ether. The product was then dried under vacuum to afford a brownish gray solid. ^1H NMR (d_6-DMSO): δ 6.79 (br s, 2H), 6.85 (s, 1H), 7.11 (br s, 1H), 7.48-7.71 (m + br s, 3H), 7.75 (t, 1H, J = 7.5 Hz), 7.81 (d, 1H, J = 7.8 Hz), 10.85 (s, 1H), 11.36 (s, 1H). ESI mass spectrum for $C_{14}H_{12}F_3N_4O_3S^+$: 373 (M + 1).

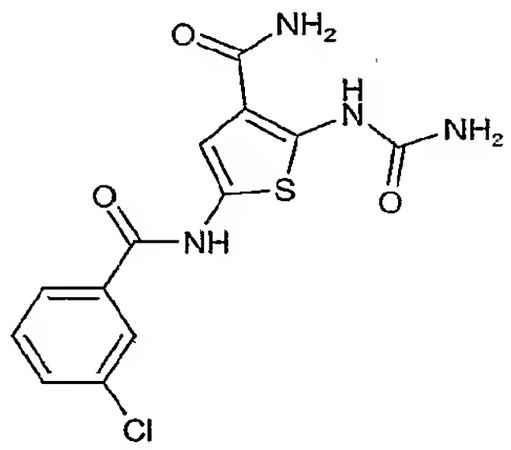
[00414] Example 42: 2-[(Aminocarbonyl)amino]-5-[(2-chlorobenzoyl)amino]thiophene-3-carboxamide



[00415]

[00416] Prepared according to Example 40 (substituting 2-chlorobenzoic acid for the m-anisic acid), except that stirring was maintained for 3.5 hrs., and after the initial water trituration, the residue was then triturated in 13 wt% aqueous K_2CO_3 solution, $CDCl_3$, and finally diethyl ether. The solid was then dissolved in DMF, added to H_2O, and the precipitate filtered, washed with H_2O, and then dried under vacuum to afford a gray solid. ^1H NMR (d_6-DMSO): δ 6.80 (br s, 2H), 6.86 (s, 1H), 7.12 (br s, 1H), 7.37-7.70 (m + br s, 5H), 10.85 (s, 1H), 11.30 (s, 1H). ESI mass spectrum for $C_{13}H_{12}ClN_4O_3S^+$ 339 (M + 1).

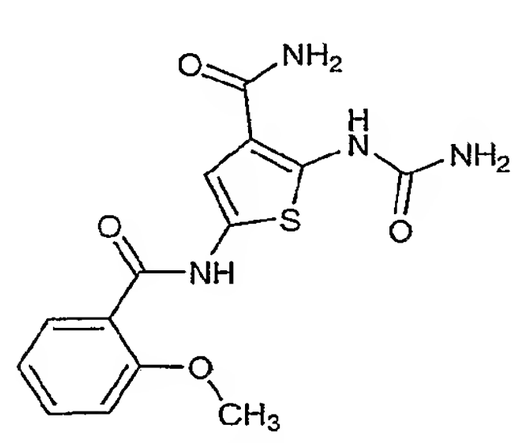
[00417] Example 43: 2-[(Aminocarbonyl)amino]-5-[(3-chlorobenzoyl)amino]thiophene-3-carboxamide



[00418]

[00419] Prepared according to Example 40 (substituting 3-chlorobenzoic acid for the m-anisic acid). The title compound is a light tan solid. ^1H NMR (d_6-DMSO): δ 6.79 (br s, 2H), 6.96 (s, 1H), 7.14 (br s, 1H), 7.45-7.73 (m + br s, 3H), 7.89 (d, 1H, J = 7.8 Hz), 7.98 (s, 1H), 10.85 (s, 1H), 11.24 (s, 1H). HRMS $C_{13}H_{12}ClN_4O_3S^+$: theoretical: 339.0313, found: 339.0311 (M+1).

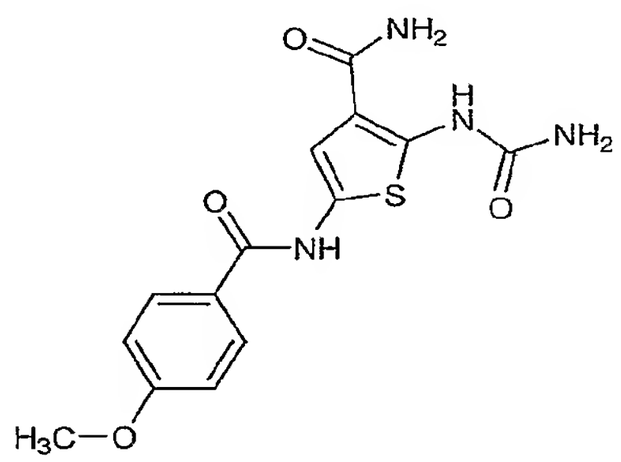
[00420] Example 44: 2-[(Aminocarbonyl)amino]-5-[(2-methoxybenzoyl)amino]thiophene-3-carboxamide



[00421]

[00422] Prepared according to Example 40 (substituting 2-methoxybenzoic acid for the m-anisic acid). The title compound is a light brown solid. ^1H NMR (d_6-DMSO): δ 3.86 (s, 3H), 6.78 (br s, 2H), 6.89 (s, 1H), 7.03 (td, 1H, J = 7.5, 0.8 Hz), 7.11 + 7.15 (overlapping br s + d, 2H, J = 8.2 Hz), 7.42-7.58 (m + br s, 2H), 7.60-7.65 (m, 1H), 10.70 (s, 1H), 10.80 (s, 1H). HRMS $C_{14}H_{15}N_4O_4S^+$: theoretical: 335.0809, found: 335.0773 (M+1).

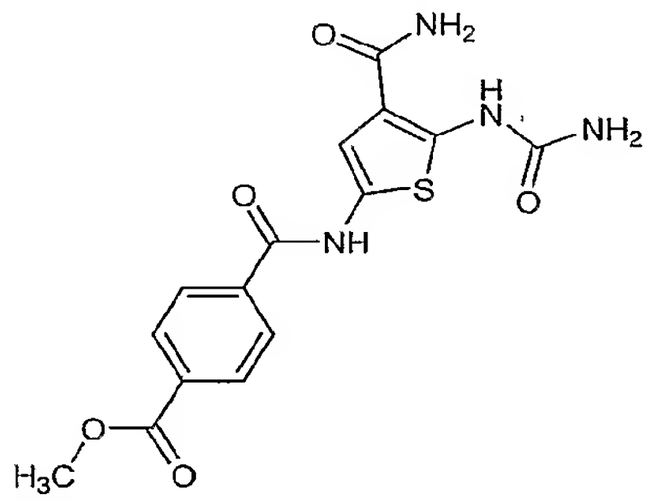
[00423] Example 45: 2-[(Aminocarbonyl)amino]-5-[(4-methoxybenzoyl)amino]thiophene-3-carboxamide



[00424]

[00425] Prepared according to Example 40 (substituting 4-methoxybenzoic acid for the m-anisic acid), except that after the K_2CO_3 trituration and water wash, the solid was then triturated in 25 mL CH_2Cl_2. The title compound is a light brown solid. ^{1}H NMR (d_6-DMSO): δ 3.80 (s, 3H), 6.76 (br s, 2H), 6.91 (s, 1H), 7.00-7.05 (m, 2H), 7.12 (br s, 1H), 7.53 (br s, 1H), 7.90-7.95 (m, 2H), 10.82 (s, 1H), 10.95 (s, 1H). HRMS $C_{14}H_{15}N_4O_4S^+$: theoretical: 335.0809, found: 335.0803 (M+1).

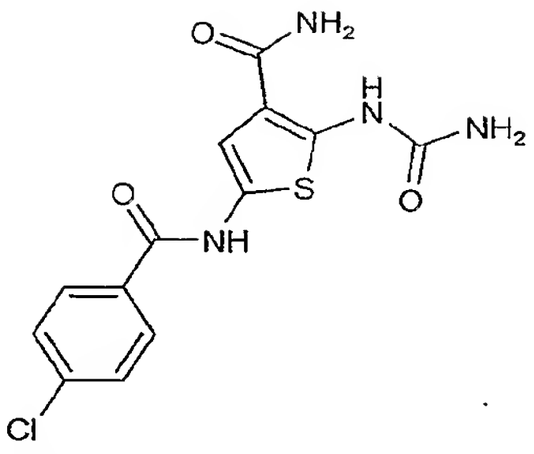
[00426] Example 46: Methyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]benzoate



[00427]

[00428] Prepared according to Example 40 (substituting 4-(methoxycarbonyl)benzoic acid for the m-anisic acid), except that after the DMF/H_2O slurry was filtered and the solid washed with 10 mL H_2O, the solid was sonicated in $CHCl_3$. After filtration, the solid was triturated in 1.0 mL DMF and most of the dissolved portion precipitated with 50 mL $CHCl_3$. After filtration the solid was triturated in 25 mL anhydrous diethyl ether followed by washing with 8 mL anhydrous diethyl ether. The product was then dried under vacuum. The title compound is a light brown solid. ^{1}H NMR (d_6-DMSO): δ 3.86 (s, 3H), 6.80 (br s, 2H), 6.99 (s, 1H), 7.16 (br s, 1H), 7.59 (br s, 1H), 8.06 (s, 4H), 10.86 (s, 1H), 11.35 (s, 1H). ESI mass spectrum for $C_{15}H_{15}N_4O_5S^+$: 363 (M + 1).

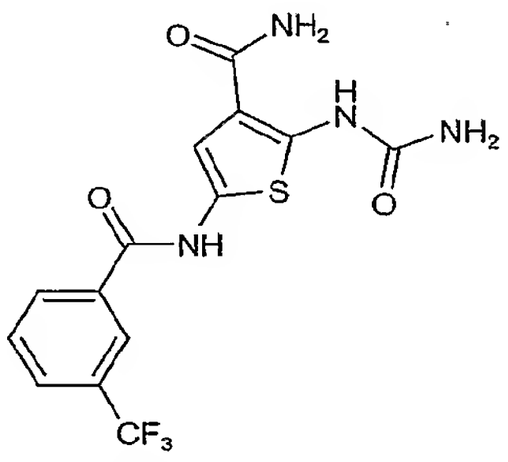
[00429] Example 47: 2-[(Aminocarbonyl)amino]-5-[(4-chlorobenzoyl)amino]thiophene-3-carboxamide



[00430] Cl

[00431] Prepared according to Example 40 (substituting 4-chlorobenzoic acid for the m-anisic acid), except that after the DMF/H_2O slurry was filtered and the solid washed with 10 mL H_2O, the solid was then sonicated in 10 mL $CHCl_3$, and then in 5 mL CH_3OH. The product was then dried under vacuum. The title compound is a brown solid. ^1H NMR (d_6-DMSO): δ 6.79 (br s, 2H), 6.96 (s, 1H), 7.15 (br s, 1H), 7.52-7.72 (m + br s, 3H), 7.97 (d, 2H, J = 8.5 Hz), 10.85 (s, 1H), 11.22 (s, 1H). ESI mass spectrum for $C_{13}H_{12}ClN_4O_3S^+$: 339 (M + 1).

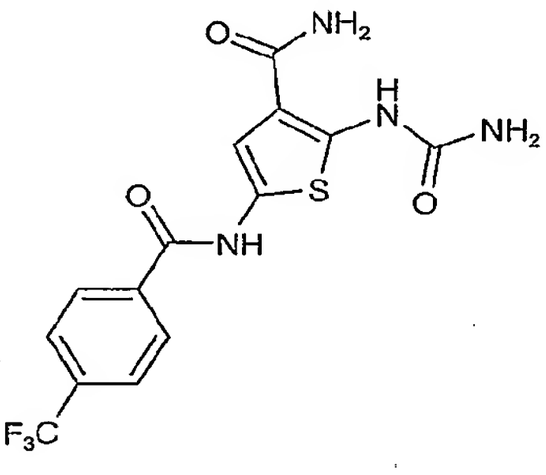
[00432] Example 48: 2-[(Aminocarbonyl)amino]-5-{[3-(trifluoromethyl)benzoyl]amino}thiophene-3-carboxamide



[00433] CF_3

[00434] Prepared according to Example 40 (substituting 3-trifluoromethylbenzoic acid for the m-anisic acid), except that after the DMF/H_2O slurry was filtered and the solid washed with 10 mL H_2O, the solid was sonicated in 10 mL $CHCl_3$. The solid was sonicated in 5 mL CH_3OH, and 3 mL H_2O was added to precipitate most of the dissolved product. The precipitate was then filtered, washed with 5 mL 1:1 CH_3OH:H_2O, and dried under vacuum. The title compound is a brown solid. ^1H NMR (d_6-DMSO): δ 6.81 (br s, 2H), 7.00 (s, 1H), 7.16 (br s, 1H), 7.59 (br s, 1H), 7.77 (t, 1H, J = 7.7 Hz), 7.94 (d, 1H, J = 7.5 Hz), 8.24 (d, 1H, J = 7.7 Hz), 8.28 (s, 1H), 10.86 (s, 1H), 11.36 (s, 1H). ESI mass spectrum for $C_{14}H_{12}F_3N_4O_3S^+$: 373 (M + 1).

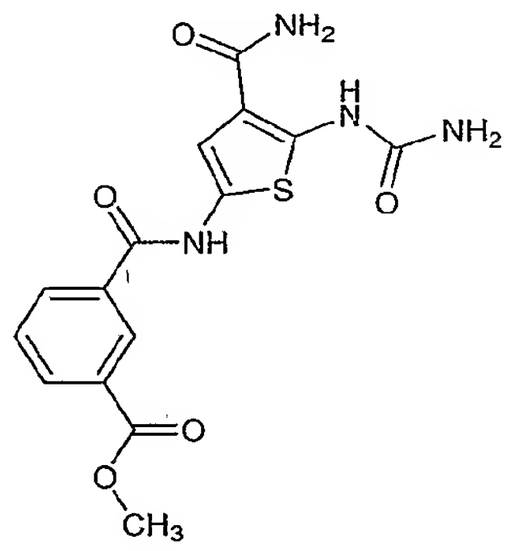
[00435] Example 49: 2-[(Aminocarbonyl)amino]-5-{[4-(trifluoromethyl)benzoyl]amino}thiophene-3-carboxamide



[00436] F_3C

[00437] Prepared according to Example 40 (substituting 4-trifluoromethylbenzoic acid for the m-anisic acid), except that after the DMF/H_2O slurry was filtered and the solid washed with 10 mL H_2O, the solid was sonicated in 10 mL $CHCl_3$. Then the solid was dissolved in 5 mL CH_3OH. H_2O (2 mL) was added to precipitate most of the dissolved product. The precipitate was then filtered, washed with 5 mL CH_3OH, dried under vacuum. The title compound is a brown solid. ^1H NMR (d_6-DMSO): δ 6.80 (br s, 2H), 7.00 (s, 1H), 7.16 (br s, 1H), 7.60 (br s, 1H), 7.90 (d, 2H, J = 8.2 Hz), 8.14 (d, 2H, J = 8.1 Hz), 10.87 (s, 1H), 11.38 (s, 1H). ESI mass spectrum for $C_{14}H_{12}F_3N_4O_3S^+$: 373 (M + 1).

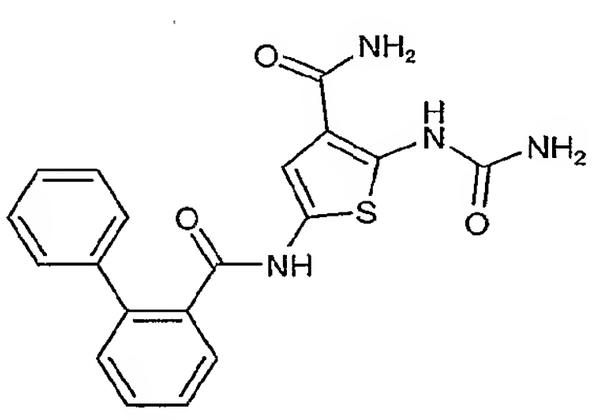
[00438] Example 50: Methyl 3-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]benzoate



[00439]

[00440] Prepared according to Example 40 (substituting 3-(methoxycarbonyl)benzoic acid for the m-anisic acid), except that the product was additionally sonicated in $CHCl_3$, filtered, partially dissolved and triturated in 1.0 mL DMF, followed by the addition of 50 mL $CHCl_3$ to precipitate the product, and then filtered. The product was then triturated in 25 mL diethyl ether, filtered, washed with 8 mL diethyl ether, sonicated in 5 mL CH_3OH, triturated in 5 mL diethyl ether, and then dried under vacuum. The title compound was a brown solid. ^1H NMR (d_6-DMSO): δ 3.90 (s, 3H), 6.82 (br s, 2H), 7.01 (s, 1H), 7.18 (br s, 1H), 7.59 (br s, 1H), 7.69 (t, 1H, J = 7.8 Hz), 8.14 (d, 1H, J = 7.9 Hz), 8.22 (d, 1H, J = 7.9 Hz), 8.55 (s, 1H), 10.86 (s, 1H), 11.37 (s, 1H). ESI mass spectrum for $C_{15}H_{15}N_4O_5S^+$: 363 (M + 1).

[00441] Example 51: 2-[(aminocarbonyl)amino]-5-[(1,1'-biphenyl-2-ylcarbonyl)amino]thiophene-3-carboxamide

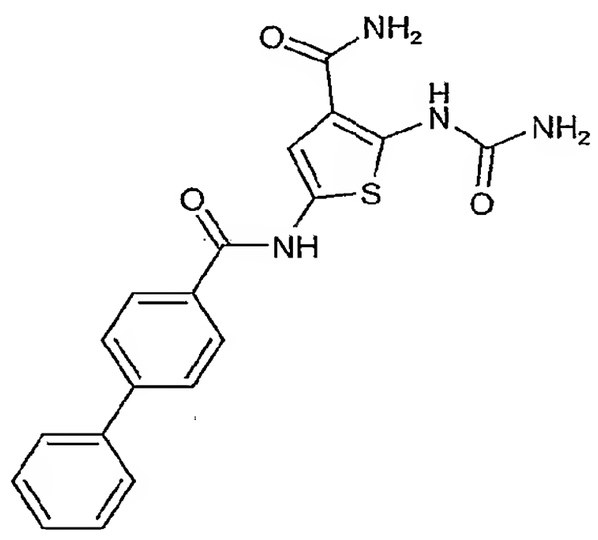


[00442]

[00443] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.428 g) (prepared according to Example 2C) was combined with 2-biphenylcarboxylic acid (0.339 g, 1.71 mmol), HATU (0.652 g, 1.71 mmol), DMF (10 mL) and triethylamine (1.6 mL, 11.5 mmol). The mixture was then stirred overnight and the DMF stripped off. The residue was triturated in 120 mL H_2O, then triturated and sonicated in 50 mL 20:80 CH_3OH:H_2O, followed by sonication in 25 mL CH_3OH, filtering, and washing with 25 mL CH_3OH. The combined methanol filtrate and wash was stripped of solvent, the residue sonicated in 100 mL H_2O, filtered, washed with 25 mL H_2O, then triturated in 50 mL

diethyl ether, triturated again in 25 mL diethyl ether, filtered, and washed with 25 mL diethyl ether. The product was then dried under vacuum. The title compound was a brown solid. ^{1}H NMR (d_6-DMSO): δ 6.70 (s, 1H), 6.76 (br s, 2H), 7.07 (br s, 1H), 7.24-7.59 (m, 10H), 10.81 (s, 1H), 11.09 (s, 1H). ESI mass spectrum for $C_{19}H_{17}N_4O_3S^+$: 381 (M + 1).

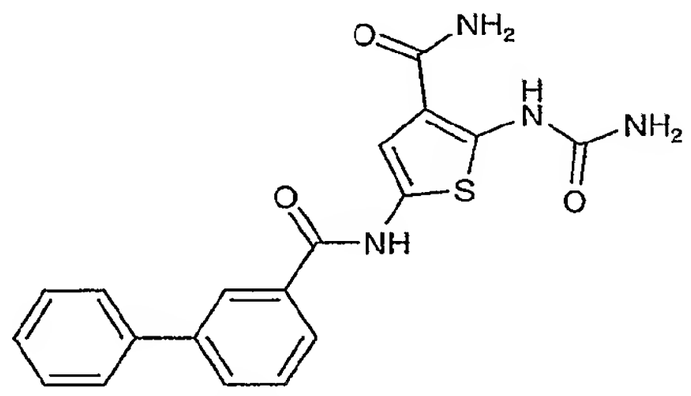
[00444] Example 52: 2-[(Aminocarbonyl)amino]-5-[(1,1'-biphenyl-4-ylcarbonyl)amino]thiophene-3-carboxamide



[00445]

[00446] Prepared according to Example 51 (substituting 4-biphenylcarboxylic acid for the 2-biphenylcarboxylic acid), except the combined methanol filtrate and wash were discarded and the solid was then sonicated in 100 mL H_2O, filtered, and washed with 25 mL H_2O. Then the solid was sonicated in 50 mL $CHCl_3$, filtered, washed with 15 mL $CHCl_3$, sonicated with 30 mL saturated sodium bicarbonate solution, filtered, washed twice with 30 mL H_2O, sonicated again with 25 mL saturated sodium bicarbonate solution, filtered, and washed with 20 mL H_2O. The product was then dried under vacuum to afford a brown solid. ^{1}H NMR (d_6-DMSO): δ 6.79 (br s, 2H), 6.98 (s, 1H), 7.14 (br s, 1H), 7.37-7.43 (m, 1H), 7.46-7.52 (m, 2H), 7.58 (br s, 1H), 7.71-7.77 (m, 2H), 7.82 (d, 2H, J = 8.6 Hz), 8.05 (d, 2H, J = 8.5 Hz), 10.85 (s, 1H), 11.20 (s, 1H). ESI mass spectrum for $C_{19}H_{17}N_4O_3S^+$: 381 (M + 1).

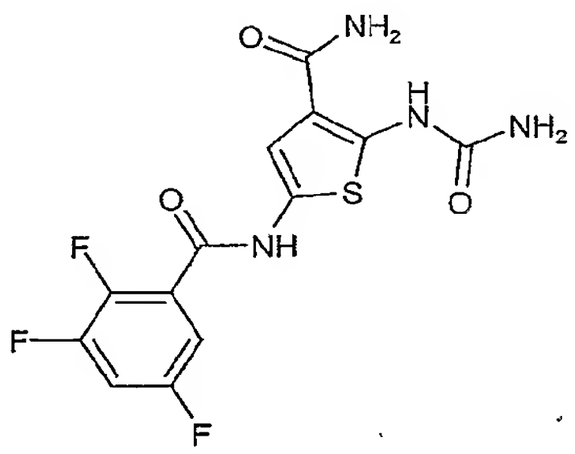
[00447] Example 53: 2-[(Aminocarbonyl)amino]-5-[(1,1'-biphenyl-3-ylcarbonyl)amino]thiophene-3-carboxamide



[00448]

[00449] Prepared according to Example 51 (substituting 3-biphenylcarboxylic acid for the 2-biphenylcarboxylic acid), except 0.401 g of the solid salt prepared according to Example 2C was used and the other reagents were scaled accordingly. Then, after the DMF was stripped off, the residue was sonicated in 50 mL H_2O, filtered, washed with 25 mL H_2O, sonicated with 50 mL saturated sodium bicarbonate solution, filtered, washed with 25 mL H_2O, triturated and sonicated in 25 mL CH_2Cl_2, filtered, and washed with 25 mL CH_2Cl_2. The product was then dried under vacuum to afford a brown solid. ^{1}H NMR (d_6-DMSO): δ 6.80 (br s, 2H), 7.00 (s, 1H), 7.15 (br s, 1H), 7.37-7.43 (m, 1H), 7.47-7.64 (m, 4H), 7.73-7.77 (m, 2H), 7.84-7.89 (m, 1H), 7.90-7.95 (m, 1H), 8.20-8.23 (m, 1H), 10.84 (s, 1H), 11.21 (s, 1H). ESI mass spectrum for $C_{19}H_{17}N_4O_3S^+$: 381 (M + 1).

[00450] Example 54: 2-[(Aminocarbonyl)amino]-5-[(2,3,5-trifluorobenzoyl)amino]thiophene-3-carboxamide

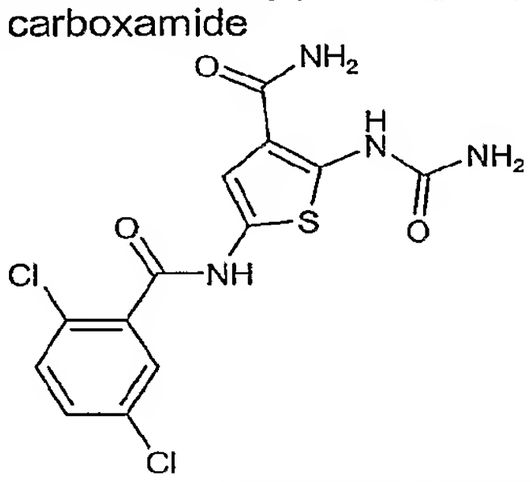


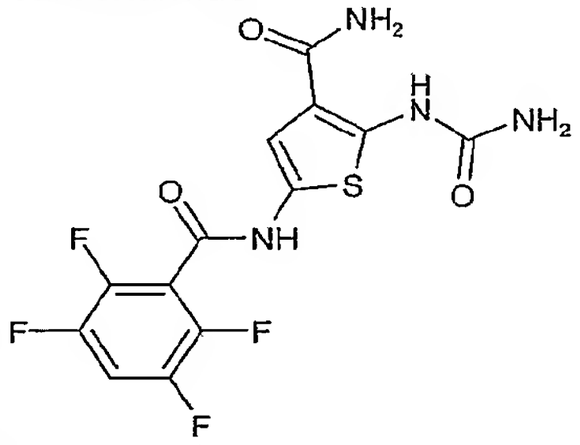
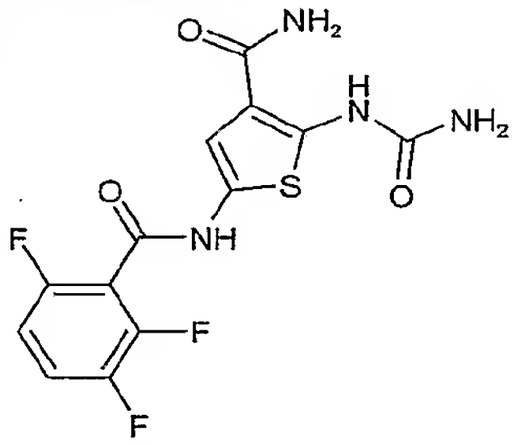
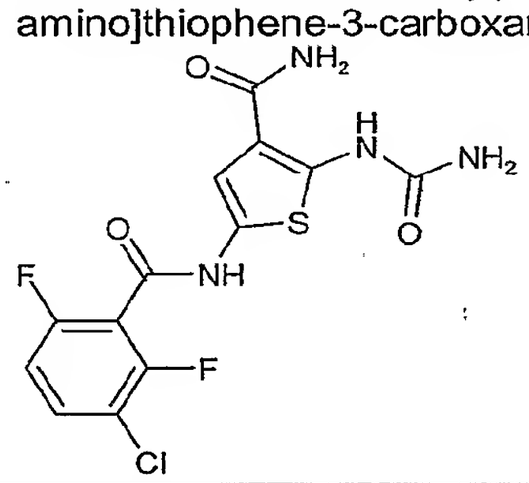
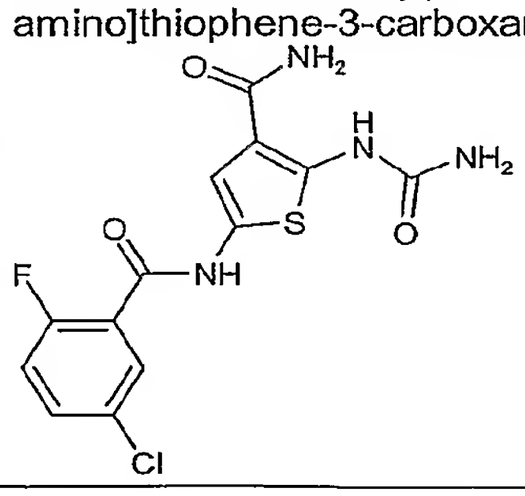
[00451]

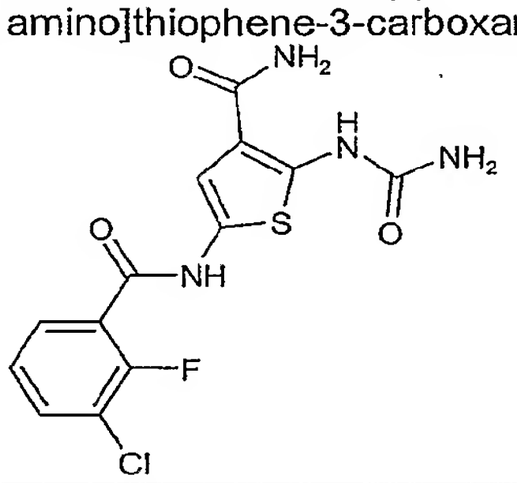
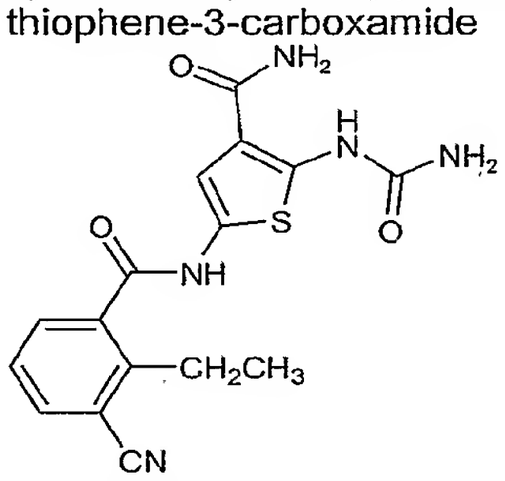
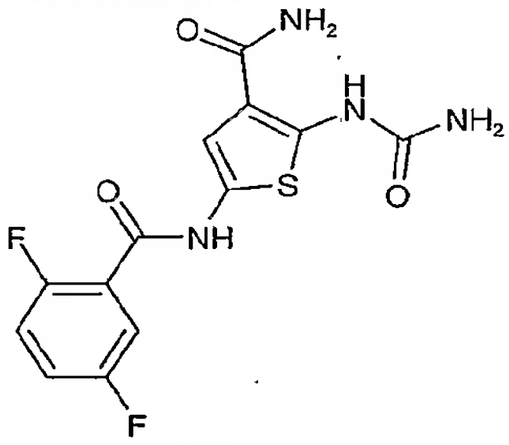
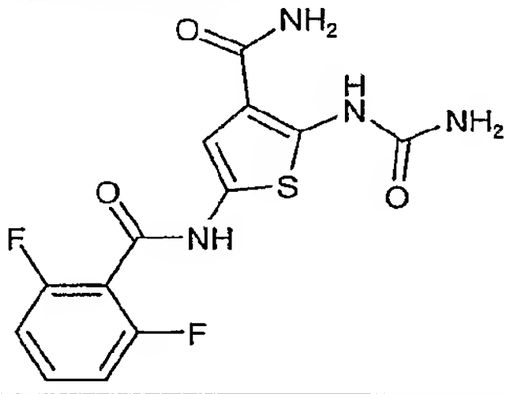
[00452] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.24 g) (prepared according to Example 2A or Example 2B) was combined with 1 mmol of 2,3,5-trifluorobenzoic acid, HBTU (BF_4) (1 mmol), N,N-dimethylethylamine (1.0 mL, 9 mmol), and DMSO (1.0 mL). The mixture was stirred for 1 hour, then most of the liquids were stripped off. The residue was triturated in 100 mL CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with H_2O (100 mL) overnight, filtered, washed with 20 mL ether, and triturated with 2 mL CH_3OH for 30 minutes. Then the product was filtered and dried under reduced pressure to afford a brown solid. ^{1}H NMR (CD_3OD): 6.89 (s, 1H), 7.28–7.36 (m, 1H), 7.37–7.45 (m, 1H). ESI mass spectrum for $C_{13}H_{10}F_3N_4O_3S^+$: 359 (M + 1).

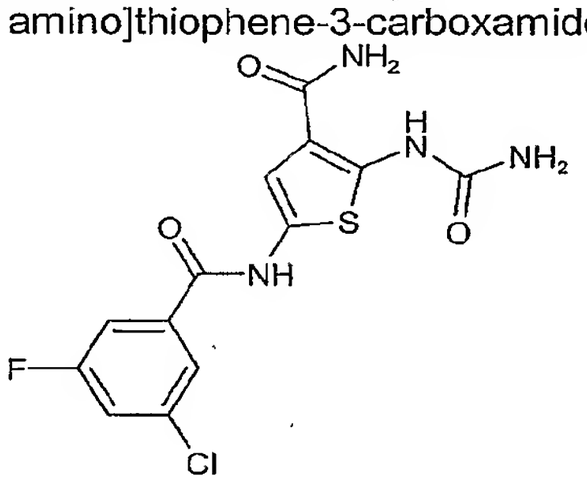
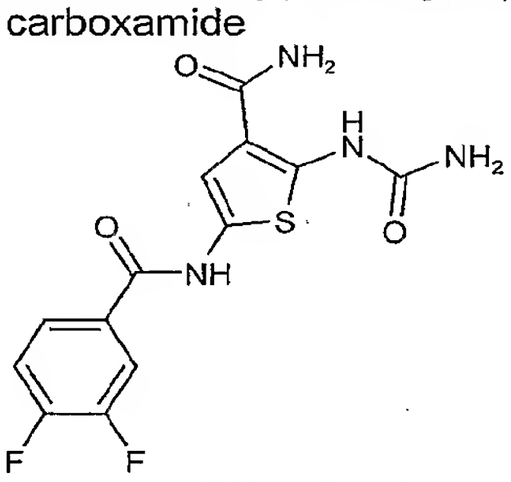
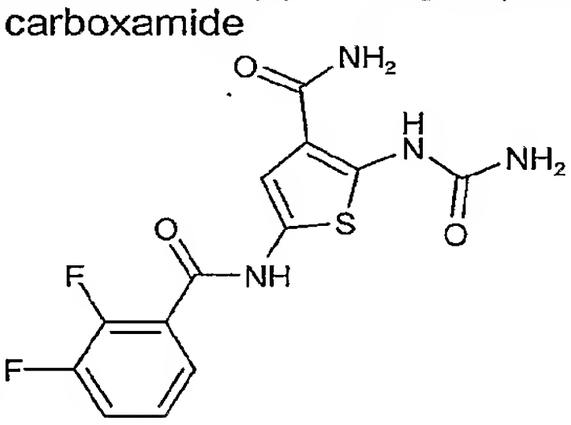
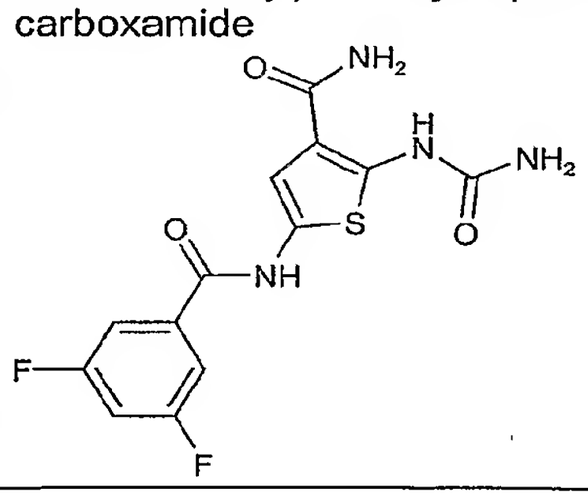
[00453] Examples 55-73, shown in Table VII below, were prepared analogously to Example 54, substituting the appropriate carboxylic acid for the 2,3,5-trifluorobenzoic acid.

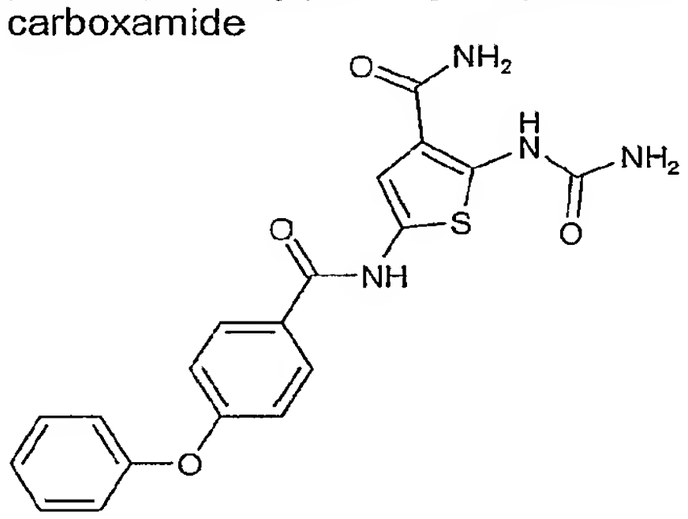
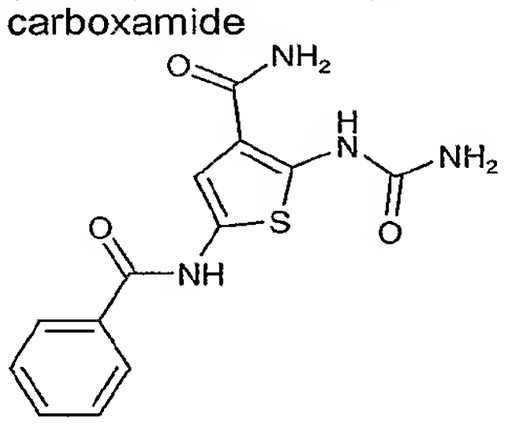
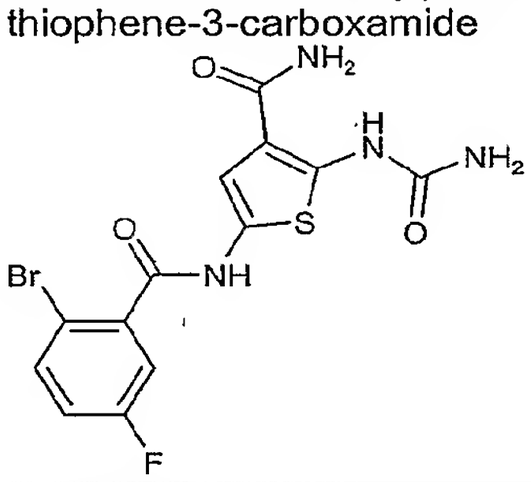
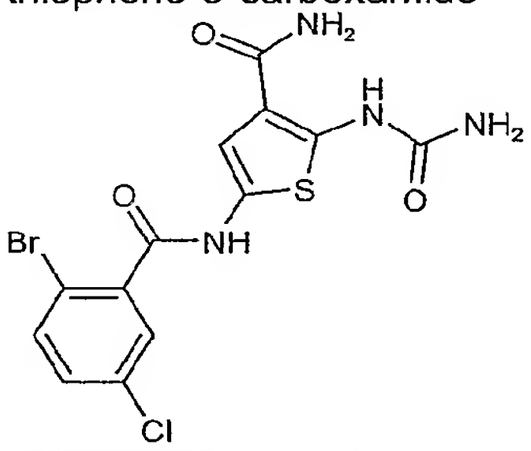
Table VII

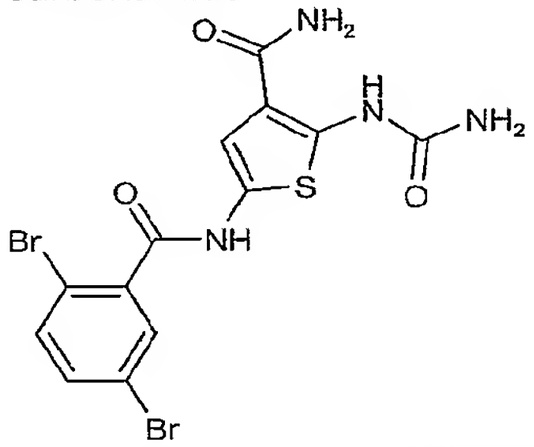
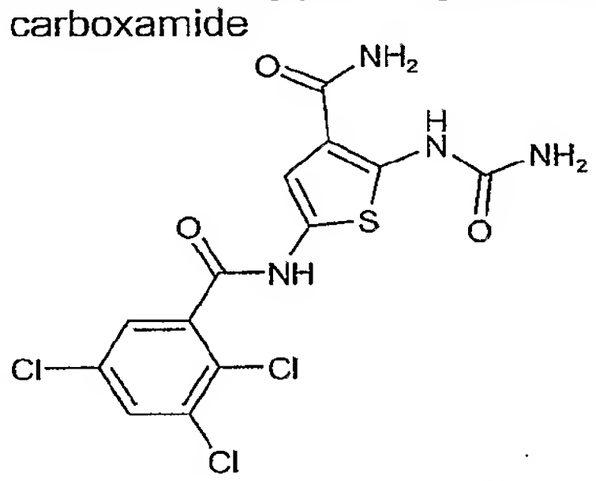
Example	Name and Structure	^{1}H NMR	MS(ES^+) (M+1)
55	2-[(Aminocarbonyl) amino]-5-[(2,5-dichlorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 6.95 (s, 1H), 7.48–7.53 (m, 2H), 7.59 (s, 1H).	373

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
56	2-[(Aminocarbonyl) amino]-5-[(2,3,5,6-tetrafluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 7.01 (s, 1H), 7.62 (tt, 1H, J = 17.5, 7.4 Hz).	377
57	2-[(Aminocarbonyl) amino]-5-[(2,3,6-trifluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 6.92 (s, 1H), 7.06–7.16 (m, 1H), 7.40–7.52 (m, 1H).	359
58	2-[(Aminocarbonyl) amino]-5-[(3-chloro-2,6-difluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 6.97 (s, 1H), 7.11–7.19 (m, 1H), 7.61–7.70 (m, 1H).	375
59	2-[(Aminocarbonyl) amino]-5-[(5-chloro-2-fluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 6.95 (s, 1H), 7.24 (t, 1H, J = 9 Hz), 7.52–7.59 (m, 1H), 7.70–7.75 (m, 1H).	357

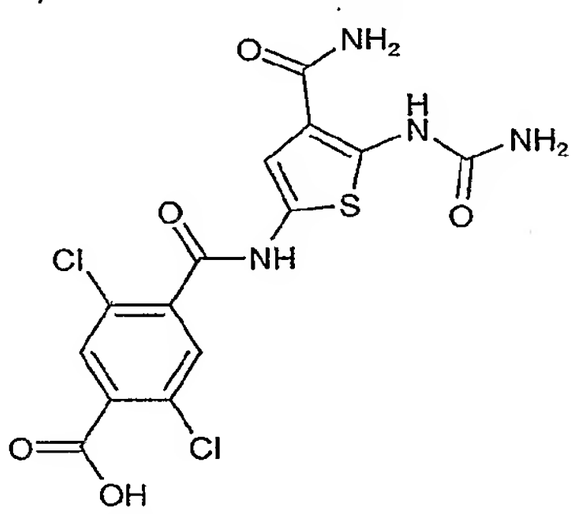
Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
60	2-[(Aminocarbonyl) amino]-5-[(3-chloro-2-fluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 6.94 (s, 1H), 7.25–7.32 (m, 1H), 7.61–7.68 (m, 2H).	357
61	2-[(Aminocarbonyl) amino]-5-[(3-cyano-2-ethylbenzoyl)amino] thiophene-3-carboxamide 	(CD_3OD): δ 1.29 (t, 3H, J = 7.5 Hz), 3.01 (q, 2H, J = 7.5 Hz), 6.94 (s, 1H), 7.49 (t, 1H, J = 7.7 Hz), 7.75 (dd, 1H, J = 7.7, 1.2 Hz), 7.82 (dd, 1H, J = 7.7, 1.2 Hz).	358
62	2-[(Aminocarbonyl) amino]-5-[(2,5-difluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 6.97 (s, 1H), 7.24–7.38 (m, 2H), 7.46–7.54 (m, 1H).	341
63	2-[(Aminocarbonyl) amino]-5-[(2,6-difluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 6.96 (s, 1H), 7.06–7.16 (m, 2H), 7.48–7.60 (m, 1H).	341

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
64	2-[(Aminocarbonyl) amino]-5-[(3-chloro-5-fluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 7.03 (s, 1H), 7.48 (d, 1H, J = 7.4 Hz), 7.68 (d, 1H, J = 7.4 Hz), 7.85 (s, 1H).	357
65	2-[(Aminocarbonyl) amino]-5-[(3,4-difluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 7.01 (s, 1H), 7.40–7.54 (m, 1H), 7.68–7.98 (m, 2H).	341
66	2-[(Aminocarbonyl) amino]-5-[(2,3-difluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 7.00 (s, 1H), 7.28–7.38 (m, 1H), 7.42–7.60 (m, 2H).	341
67	2-[(Aminocarbonyl) amino]-5-[(3,5-difluorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD): δ 6.98 (s, 1H), 7.16–7.24 (m, 1H), 7.51–7.59 (m, 2H).	341

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
68	2-[(Aminocarbonyl) amino]-5-[(4-phenoxybenzoyl)amino] thiophene-3-carboxamide 	(CD_3OD): δ 6.91 (s, 1H), 7.05–7.16 (m, 4H), 7.22–7.28 (m, 1H), 7.42–7.50 (m, 2H), 7.94–8.97 (m, 2H).	397
69	2-[(Aminocarbonyl) amino]-5-(benzoylamino) thiophene-3-carboxamide 	(CD_3OD): δ 7.00 (s, 1H), 7.52–7.66 (m, 3H), 7.92–7.99 (m, 2H).	305
70	2-[(Aminocarbonyl) amino]-5-[(2-bromo-5-fluorobenzoyl)amino] thiophene-3-carboxamide 	(CD_3OD): δ 6.95 (s, 1H), 7.19 (apparent td, 1H, J = 8.4, 3.0 Hz), 7.34 (dd, 1H, J = 5.4, 3.0 Hz), 7.70 (dd, 1H, J = 4.9, 3.9 Hz).	401
71	2-[(Aminocarbonyl) amino]-5-[(2-bromo-5-chlorobenzoyl)amino] thiophene-3-carboxamide 	(CD_3OD)/d_6-DMSO (4:1): δ 6.83 (s, 1H), 7.19 (dd, 1H, J = 6.0, 2.5 Hz), 7.41 (d, 1H, J = 2.5 Hz), 7.62 (d, 1H, J = 8.6 Hz).	417

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
72	2-[(Aminocarbonyl) amino]-5-[(2,5-dibromobenzoyl)amino]thiophene-3-carboxamide 	(CD_3OD)/d_6-DMSO (4:1): δ 6.81 (s, 1H), 7.42–7.56 (m, 2H), 7.61 (d, 1H, J = 2.2 Hz), 7.62 (d, 1H, J = 8.6 Hz).	461
73	2-[(Aminocarbonyl) amino]-5-[(2,3,5-trichlorobenzoyl) amino]thiophene-3-carboxamide 	(CD_3OD)/d_6-DMSO (4:1): δ 6.96 (s, 1H), 7.56 (d, 1H, J = 2.3 Hz), 7.78 (d, 1H, J = 2.4 Hz), 7.88 (s, 1H).	407

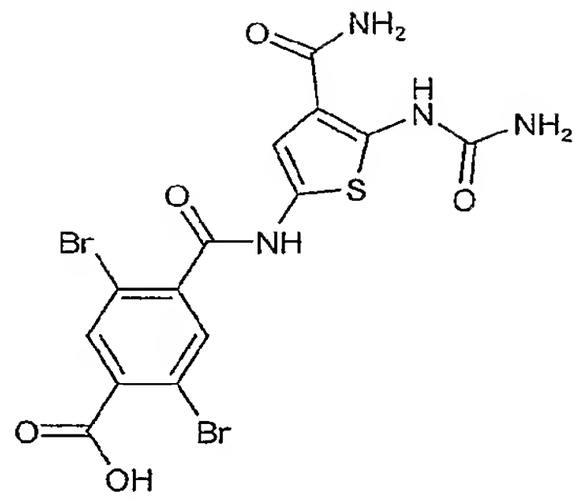
[00454] Example 74: 4-[({4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]-2,5-dichlorobenzoic acid



[00455]

[00456] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.24 g) (prepared according to Example 2A or Example 2B) was combined with 2 mmol of 2,5-dichloro-4-carboxybenzoic acid, HBTU (BF_4) (2 mmol), N,N-dimethylethylamine (2.0 mL, 18 mmol), and DMSO (2.0 mL). The mixture was stirred for 1 hour, then most of the liquids were stripped off. The residue was triturated in 100 mL CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with H_2O (100 mL) overnight, filtered, washed with 20 mL ether, and triturated with 5 mL CH_3OH for 30 minutes. Then the product was filtered and dried under reduced pressure. ^{1}H NMR (CD_3OD)/d_6-DMSO (4:1): δ 6.98 (s, 1H), 7.77 (s 1H), 7.98 (s 1H). ESI mass spectrum for $C_{14}H_{10}Cl_2N_4O_5S^+$: 417 (M + 1).

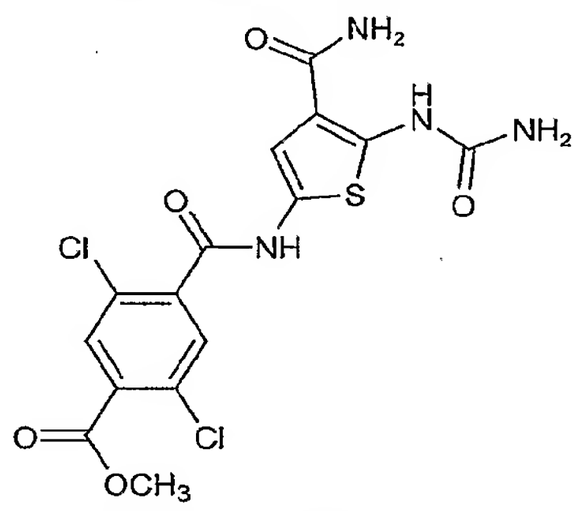
[00457] Example 75: 4-[({4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]-2,5-dibromobenzoic acid



[00458]

[00459] Prepared similarly to Example 74 (substituting 2,5-dibromo-4-carboxybenzoic acid for the 2,5-dichloro-4-carboxybenzoic acid). ^{1}H NMR (CD_3OD)/d_6-DMSO (4:1): δ 6.91 (s, 1H), 7.88 (s 1H), 7.99 (s 1H). ESI mass spectrum for $C_{14}H_{10}Br_2N_4O_5S^+$: 504 (M + 1).

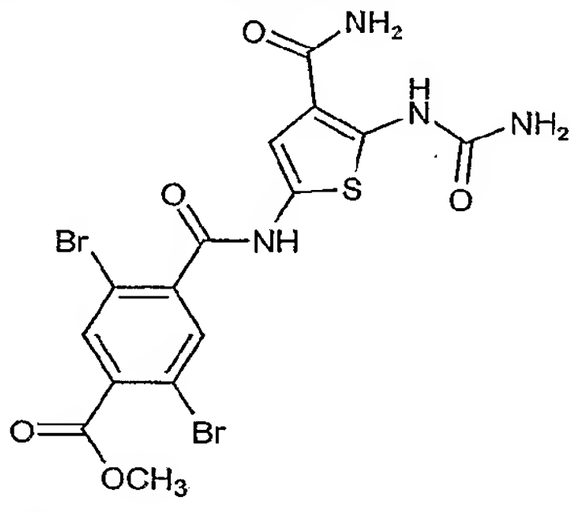
[00460] Example 76: Methyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]-2,5-dichlorobenzoate



[00461]

[00462] 4-[({4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]-2,5-dichlorobenzoic acid (Example 74 0.2 mmol) was combined with 0.1 mL (2.5 mmol) of CH_3OH, HBTU (BF_4) (0.3 mmol), N,N-dimethylethylamine (0.2 mL, 2 mmol), and DMSO (0.6 mL). The mixture was stirred for 1 hour, then most of the liquids were stripped off. The residue was triturated in 100 mL CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with H_2O (100 mL) overnight, filtered, washed with 20 mL ether, and triturated with 5 mL CH_3OH for 30 minutes. Then the product was filtered and dried under reduced pressure. ^{1}H NMR (CD_3OD)/d_6-DMSO (4:1): δ 3.82 (s, 3H), 6.88 (s, 1H), 7.68 (s 1H), 7.88 (s 1H). ESI mass spectrum for $C_{15}H_{12}Cl_2N_4O_5S^+$: 431 (M + 1).

[00463] Example 77: Methyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]-2,5-dibromobenzoate

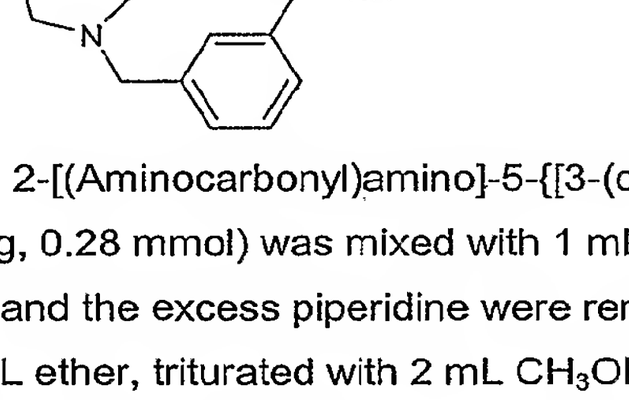


[00464]

[00465] Prepared according to Example 76 (substituting 4-[({4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]-2,5-dibromobenzoic acid (Example 75) for the 4-[({4-

(Aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]-2,5-dichlorobenzoic acid). ^{1}H NMR (CD_3OD)/d_6-DMSO (4:1): δ 3.83 (s, 3H), 6.83 (s, 1H), 7.79 (s 1H), 7.98 (s 1H). ESI mass spectrum for $C_{15}H_{12}Br_2N_4O_5S^+$: 519 (M + 1).

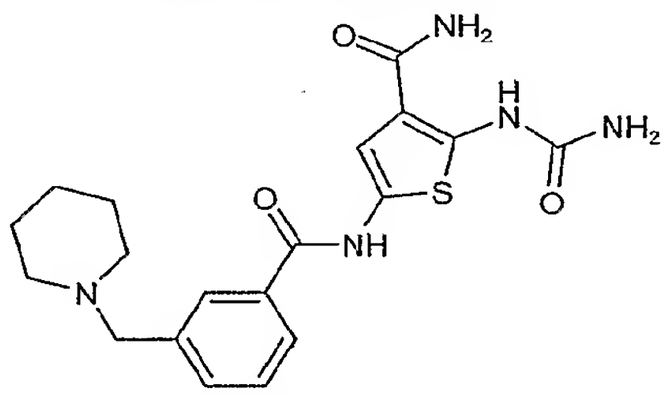
[00466] Example 78: 2-[(Aminocarbonyl)amino]-5-{[3-(chloromethyl)benzoyl]amino}thiophene-3-carboxamide



[00467]

[00468] Made similarly to Example 54 (substituting 3-chloromethylbenzoic acid for the 2,3,5-trifluorobenzoic acid), except that instead of N,N-dimethylethylamine, 1 mL N,N-diisopropylethylamine was used. ^{1}H NMR (CD_3OD): δ 4.75 (s, 2H), 6.97 (s, 1H), 7.54 (t, 1H, J = 7.6 Hz), 7.66 (d, 1H, J = 7.7 Hz), 7.88 (d, 1H, J = 7.8 Hz), 7.88 (s, 1H). ESI mass spectrum for $C_{14}H_{13}ClN_4O_3S^+$: 353 (M + 1).

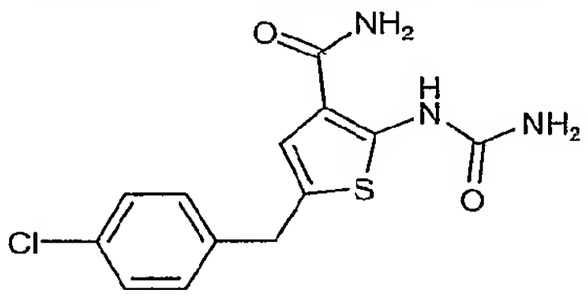
[00469] Example 79: 2-[(Aminocarbonyl)amino]-5-{[3-(piperidin-1-ylmethyl)benzoyl]amino}thiophene-3-carboxamide



[00470]

[00471] 2-[(Aminocarbonyl)amino]-5-{[3-(chloromethyl)benzoyl]amino}thiophene-3-carboxamide (Example 78, 0.1 g, 0.28 mmol) was mixed with 1 mL piperidine and 1 mL DMF, and heated overnight with stirring. The DMF and the excess piperidine were removed under reduced pressure, the residue was washed with 10 mL ether, triturated with 2 mL CH_3OH, then filtered and dried. ^{1}H NMR (CD_3OD): δ 1.20-2.00 (m, 6H), 4.18 (s, 2H), 2.61-2.99 (m, 2H), 3.20-3.43 (m, 2H), 6.68 (s, 1H), 7.35-7.45 (m, 1H), 7.46-7.56 (m, 1H), 7.60-7.74 (m, 2H). ESI mass spectrum for $C_{19}H_{23}N_5O_3S^+$: 402 (M + 1).

[00472] Example 80: 2-[(aminocarbonyl)amino]-5-(4-chlorobenzyl)thiophene-3-carboxamide



[00473]

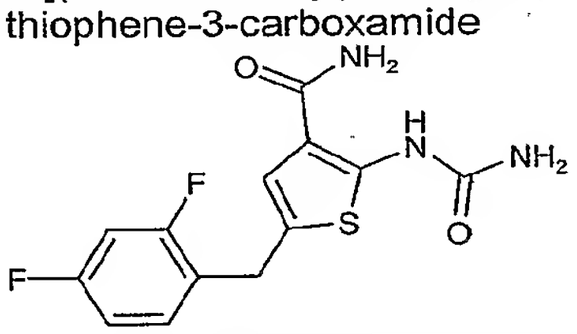
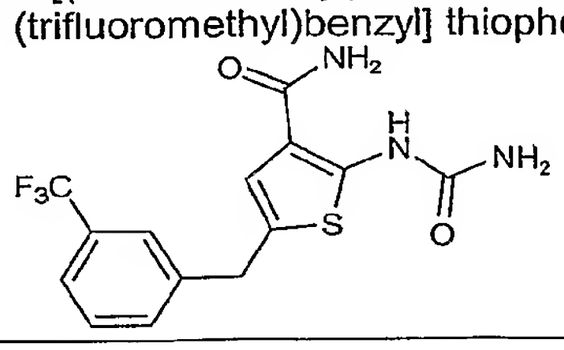
[00474] To 0.150 g (0.568 mmol) of 2-[(aminocarbonyl)amino]-5-bromothiophene-3-carboxamide was added 0.013 g (0.057 mmol) of palladium (II) acetate, 0.030 g (0.114 mmol) triphenylphosphine, and 11.36 mL (5.680 mmol) of a 0.5M solution of 4-chlorobenzylzinc chloride. The reaction mixture was heated under nitrogen to 40°C overnight and the reaction progress was monitored by

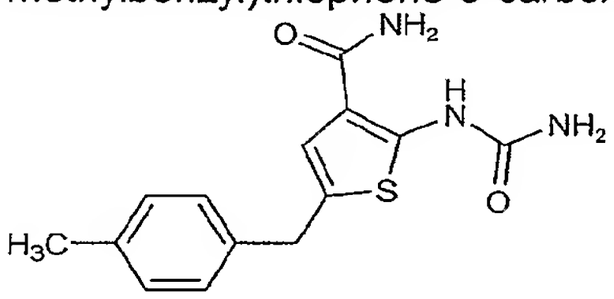
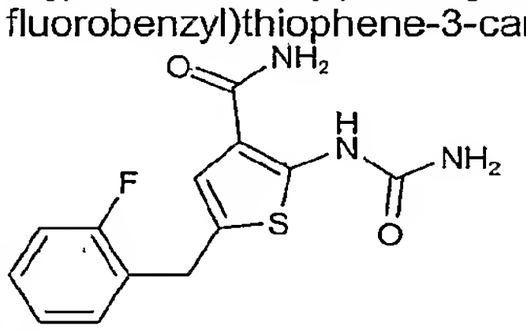
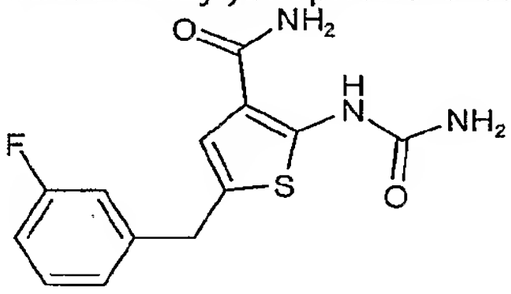
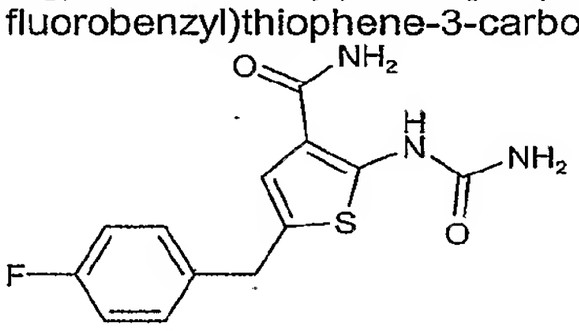
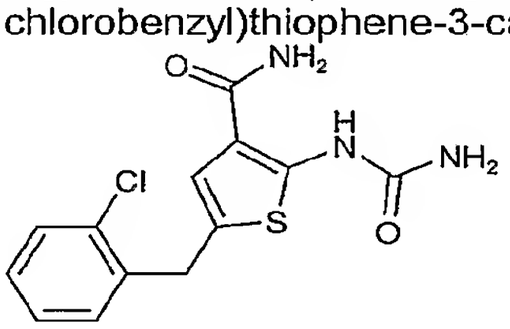
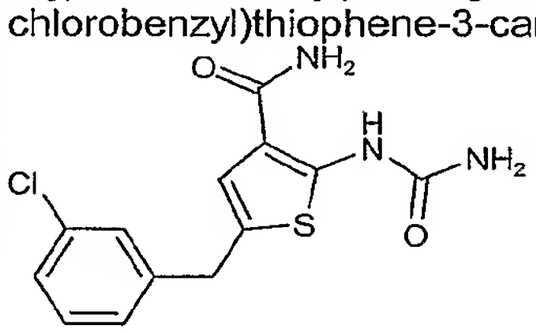
HPLC. Quenched reaction mixture with 10 mL 2N HCl and added 30 mL ethyl acetate and 20 mL H_20. The organic layer was washed with H_2O, dried over Na_2SO4, filtered, and concentrated to afford a yellow oil which was purified by reverse phase chromatography. Concentration of the desired fractions afforded a yellow solid. ^1H NMR (d_6-DMSO/400 MHz) δ 3.92 (s, 2H), 6.80 (br s, 2H), 7.00 (s, 1H), 7.12 (br s, 1H), 7.24 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.0Hz), 7.53 (br s, 1H), 10.86 (s, 1H). HRMS $C_{13}H_{13}ClN_3O_2S^+$: theoretical 310.0412, found 310.0405.

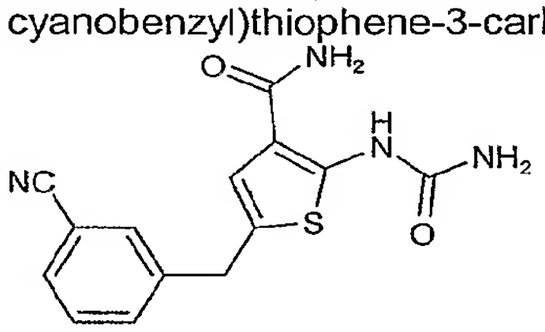
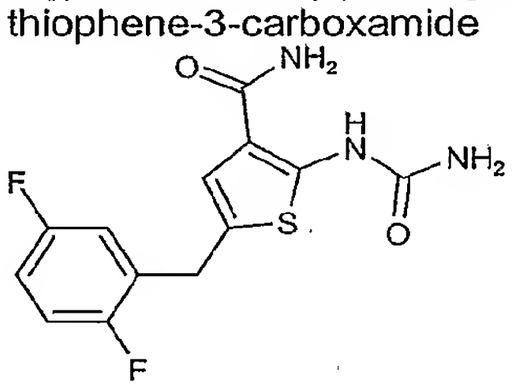
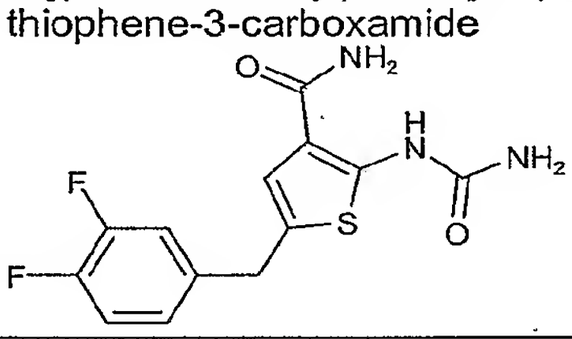
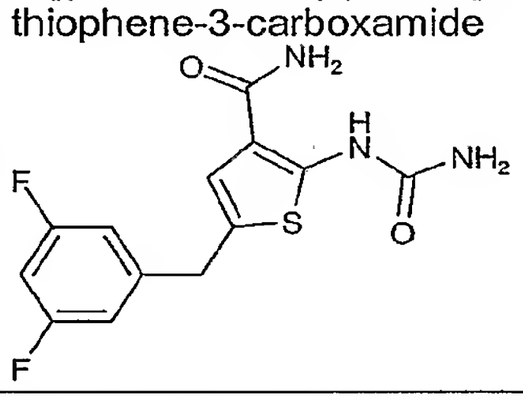
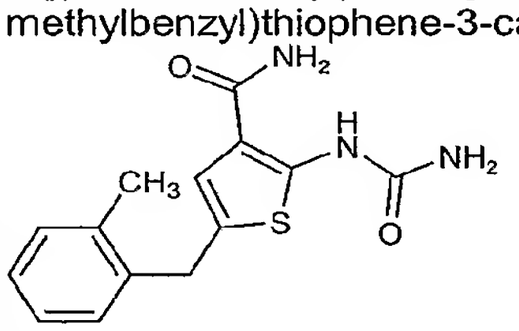
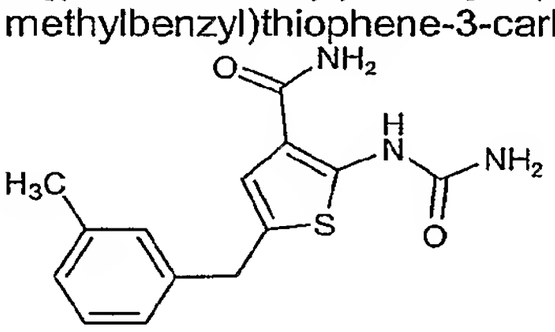
[00475] Examples 81-100 (shown in Table VIII, below) were prepared by parallel synthesis, substituting the appropriate zinc chloride reagent. The parallel synthesis apparatus consists of an aluminum block, which can be heated or cooled to the appropriate temperature, with a set of wells for 20–50 mL glass vessels. The parallel reactor blocks can be used under reflux conditions and inert atmosphere (obtained from J-KEM Scientific, Inc., St. Louis, MO, USA or ChemGlass Inc., Vineland, NJ, USA).

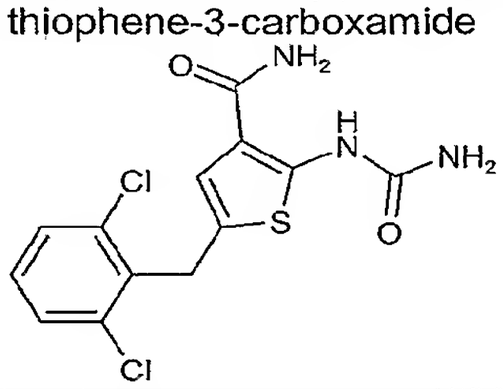
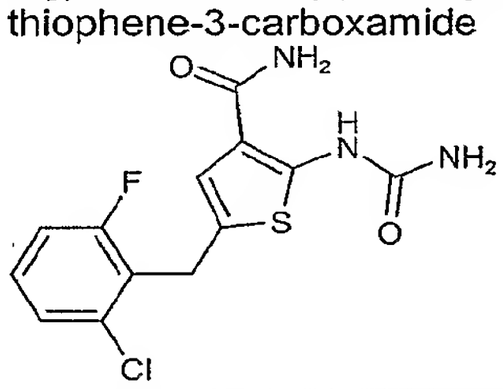
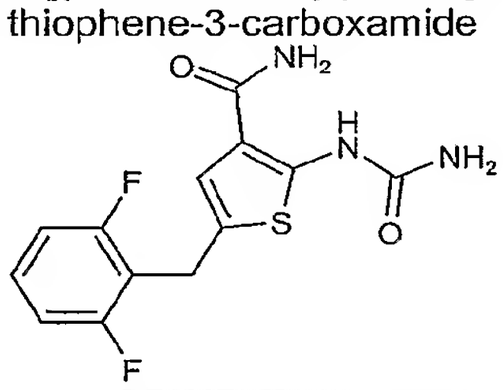
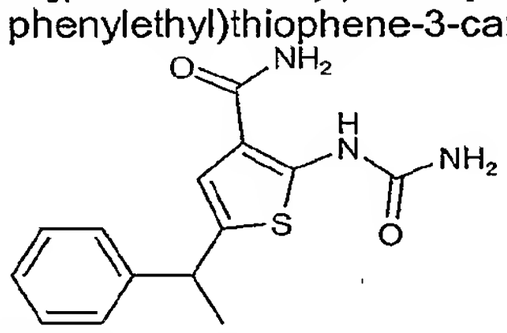
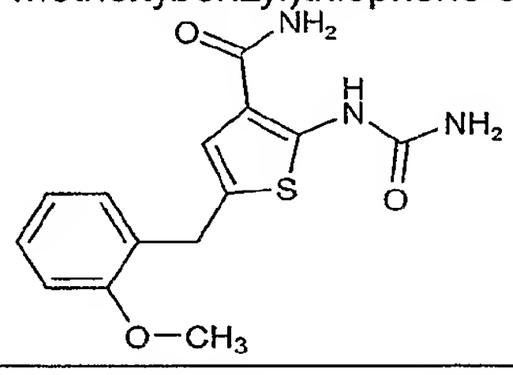
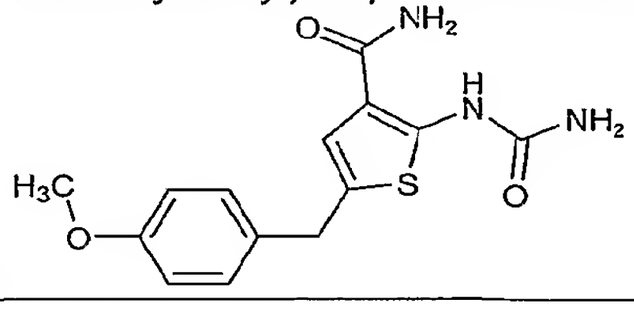
[00476] Analytical LCMS reverse phase chromatography was carried out using a C18 column 2.1 mm inner diameter x 30 mm and a linear gradient of 5% acetonitrile in 0.1% TFA/H_2O to 95% acetonitrile in 0.1% TFA/H_2O over 4.5 min. at a flow rate of 1 mL/min. The eluent composition was held at 95% acetonitrile in 0.1% TFA/H_2O from 4.5 min to 6 min. The LCMS was equipped with a diode array detector, a mass spectral detector (MSD) and an evaporative light scattering detector (ELS). A flow splitter was attached after the UV diode array detector to allow flow to the MSD and ELS. Mass spectra were obtained using an Agilent MSD in electrospray positive mode. Preparative reverse phase chromatography was carried out using a C18 column 41.4 mm i.d. of 50 mm, 100 mm or 300 mm length. The HPLC retention time was determined using analytical LCMS reverse phase analysis and represents the time obtained for the compound having the desired molecular ion. The retention time is based on the observed time in the UV chromatogram. The molecular ion listed in the table is the baseline (100%) peak, unless otherwise noted. Purity of the compounds prepared by parallel synthesis was determined by detection of the peak of the desired molecular ion and integration of the corresponding peak detected either by UV at 254 nm or by ELS.

Table VIII

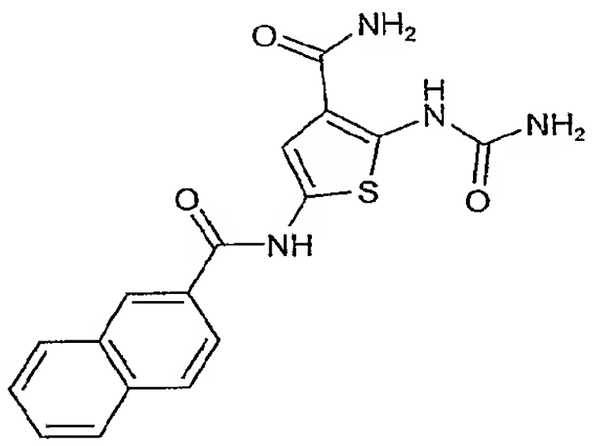
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
81	2-[(aminocarbonyl)amino]-5-(2,4-difluorobenzyl) thiophene-3-carboxamide 	2.421	312	312.0625
82	2-[(aminocarbonyl)amino]-5-[3-(trifluoromethyl)benzyl] thiophene-3-carboxamide 	2.647	344	344.068

Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
83	2-[(aminocarbonyl)amino]-5-(4-methylbenzyl)thiophene-3-carboxamide 	2.469	290	290.0926
84	2-[(aminocarbonyl)amino]-5-(2-fluorobenzyl)thiophene-3-carboxamide 	2.283	294	294.0751
85	2-[(aminocarbonyl)amino]-5-(3-fluorobenzyl)thiophene-3-carboxamide 	2.265	294	294.074
86	2-[(aminocarbonyl)amino]-5-(4-fluorobenzyl)thiophene-3-carboxamide 	2.265	294	294.0746
87	2-[(aminocarbonyl)amino]-5-(2-chlorobenzyl)thiophene-3-carboxamide 	2.396	310	310.0421
88	2-[(aminocarbonyl)amino]-5-(3-chlorobenzyl)thiophene-3-carboxamide 	2.457	310	310.0453

Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
89	2-[(aminocarbonyl)amino]-5-(3-cyanobenzyl)thiophene-3-carboxamide 	2.116	301	301.0792
90	2-[(aminocarbonyl)amino]-5-(2,5-difluorobenzyl) thiophene-3-carboxamide 	2.289	312	312.0609
91	2-[(aminocarbonyl)amino]-5-(3,4-difluorobenzyl) thiophene-3-carboxamide 	2.35	312	
92	2-[(aminocarbonyl)amino]-5-(3,5-difluorobenzyl) thiophene-3-carboxamide 	2.353	312	312.0631
93	2-[(aminocarbonyl)amino]-5-(2-methylbenzyl)thiophene-3-carboxamide 	2.371	290	290.0928
94	2-[(aminocarbonyl)amino]-5-(3-methylbenzyl)thiophene-3-carboxamide 	2.415	290	290.097

Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
95	2-[(aminocarbonyl)amino]-5-(2,6-dichlorobenzyl) thiophene-3-carboxamide 	2.583	344	344.0015
96	2-[(aminocarbonyl)amino]-5-(2-chloro-6-fluorobenzyl) thiophene-3-carboxamide 	2.423	328	328.0315
97	2-[(aminocarbonyl)amino]-5-(2,6-difluorobenzyl) thiophene-3-carboxamide 	2.272	312	312.0622
98	2-[(aminocarbonyl)amino]-5-(1-phenylethyl)thiophene-3-carboxamide 	2.355	290	290.097
99	2-[(aminocarbonyl)amino]-5-(3-methoxybenzyl)thiophene-3-carboxamide 	2.273	306	306.0909
100	2-[(aminocarbonyl)amino]-5-(4-methoxybenzyl)thiophene-3-carboxamide 	2.202	306	306.0907

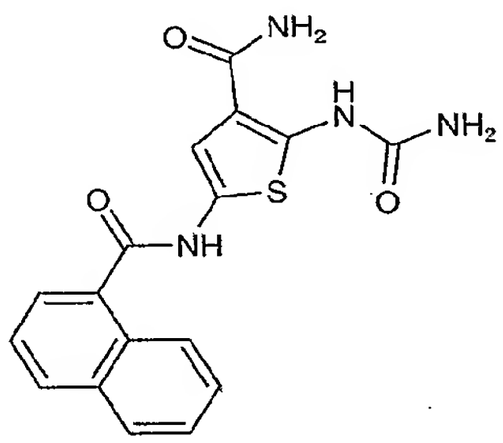
[00477] Example 101: 2-[(aminocarbonyl)amino]-5-(2-naphthoylamino)thiophene-3-carboxamide



[00478]

[00479] The solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.428 g) (prepared according to Example 2C) was combined with 2-naphthoic acid (0.296 g, 1.72 mmol), HATU (0.652 g, 1.71 mmol), DMF (10 mL) and triethylamine (1.6 mL, 11.5 mmol). The mixture was then stirred overnight and the DMF stripped off. The residue was triturated in 120 mL H_2O, then triturated and sonicated in 50 mL 20:80 CH_3OH:H_2O, followed by two cycles of sonication in 25 mL CH_3OH, filtering, and washing with 25 mL CH_3OH. The product was then dried under vacuum. ^1H NMR (d_6-DMSO): δ 6.80 (br s, 2H), 7.01 (s, 1H), 7.16 (br s, 1H), 7.56-7.66 (m, 3H), 7.96-8.08 (m, 4H), 8.56 (s, 1H), 10.86 (s, 1H), 11.30 (s, 1H). ESI Mass Spectrum $C_{17}H_{15}N_4O_3S^+$: 355 (M + 1).

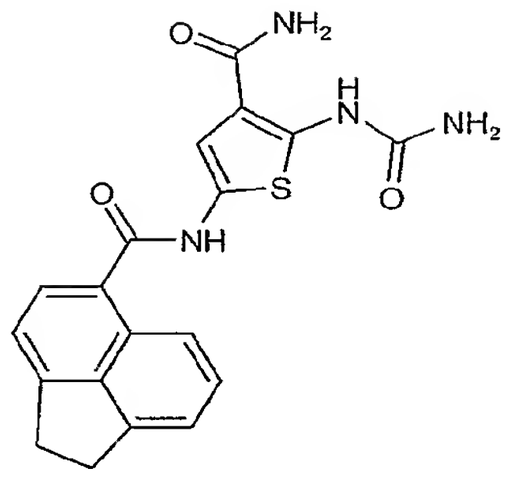
[00480] Example 102: 2-[(aminocarbonyl)amino]-5-(1-naphthoylamino)thiophene-3-carboxamide



[00481]

[00482] Prepared similarly to Example 101 (substituting 1-naphthoic acid (0.295 g, 1.71 mmol) for the 2-naphthoic acid), except that after sonication once in 25 mL CH_3OH, filtering, and washing with 25 mL CH_3OH, the methanol filtrate and wash were combined with 25 mL H_2O and then partially stripped to remove some of the methanol. The resulting precipitate was filtered and washed with 25 mL H_2O, then sonicated in 15 mL CH_3OH, 30 mL H_2O was added, the precipitate filtered, washed with H_2O, and dried under vacuum. ^1H NMR (d_6-DMSO): δ 6.81 (br s, 2H), 6.91 (s, 1H), 7.14 (br s, 1H), 7.54-7.63 (m, 4H), 7.72 (dd, 1H, J = 7.1 Hz, J = 1.2 Hz), 7.98-8.02 (m, 1H), 8.06 (d, 1H, J = 8.3 Hz), 8.14-8.19 (m, 1H), 10.88 (s, 1H), 11.40 (s, 1H). ESI Mass Spectrum $C_{17}H_{15}N_4O_3S^+$: 355 (M + 1).

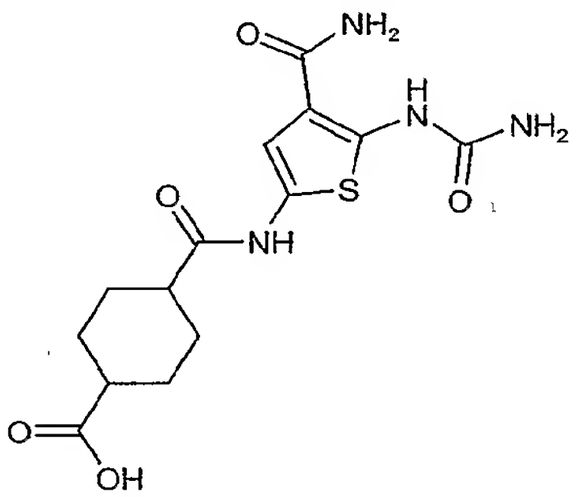
[00483] Example 103: 2-[(aminocarbonyl)amino]-5-[(1,2-dihydroacenaphthylen-5-ylcarbonyl)amino]thiophene-3-carboxamide



[00484]

[00485] Prepared analogously to Example 101. ^{1}H NMR (CD_3OD/d_6-DMSO (4:1)): δ 3.38 (s, 4H), 6.84 (s, 1H), 7.32 (d, 2H, J = 7.04 Hz), 7.49 (t, 1H, J = 6.95 Hz), 7.76 (d, 1H, J = 7.15 Hz), 8.46 (d, 1H, J = 8.46 Hz). Mass of Molecular Ion: 381 (M + 1).

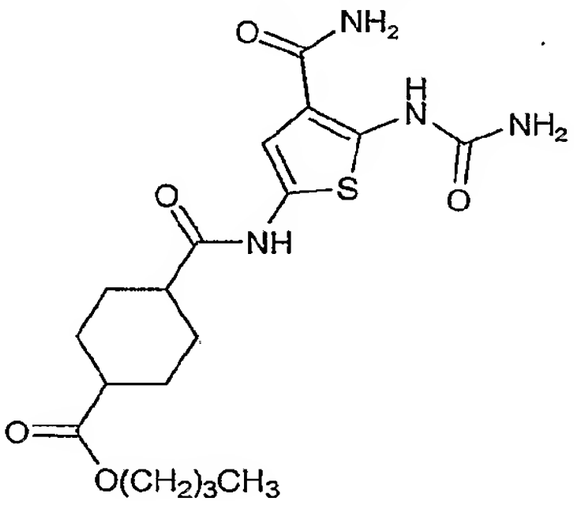
[00486] Example 104: 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]cyclohexane carboxylic acid



[00487]

[00488] The solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.15 g) (prepared according to either Example 2A or Example 2B) was combined with 0.18 g (1.045 mmol) of trans-1,4-cyclohexanedicarboxylic acid, HBTU (BF_4) (0.32 g, 1 mmol), N,N-dimethylethylamine (1.6 mL) and DMSO (1.5 mL). The mixture was stirred for 1 hour, then most of the liquids were stripped off. The residue was triturated in 100 mL CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with H_2O (100 mL) overnight, filtered, washed with 20 mL ether, and triturated with 5 mL CH_3OH for 30 minutes. Then the product was filtered and dried under reduced pressure to give the product. ^{1}H NMR (CD_3OD/d_6-DMSO(4:1)): δ 1.39–1.69 (m, 4H), 1.90–2.12 (m, 4H), 2.22–2.44 (m, 2H), 6.90 (s, 1H). ESI Mass Spectrum $C_{14}H_{19}N_4O_5S^+$: 355 (M + 1).

[00489] Example 105: Butyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]cyclohexane carboxylate

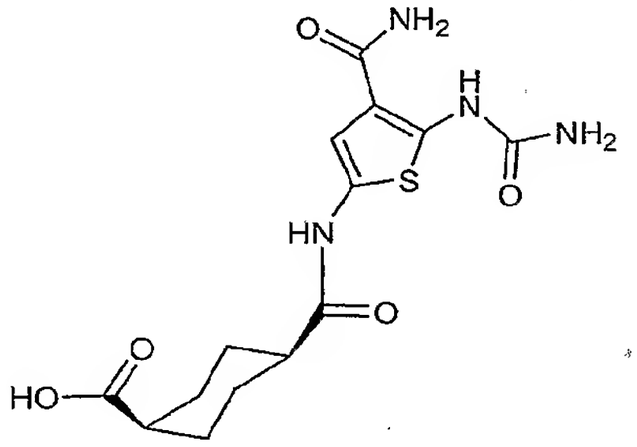


[00490]

[00491] 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]cyclohexanecarboxylic acid (Example 115, 0.12 g, 0.34 mmol) was combined with 0.1 mL (2.5 mmol) of CH_3OH, HBTU (BF_4) 0.17 g (0.5 mmol), N,N-dimethylethylamine (0.7 mL), and DMSO (1.0 mL). The mixture was stirred overnight, then most of the liquids were stripped off. The residue was triturated in 100 mL CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with H_2O (100 mL) overnight, filtered, triturated with 50 mL a saturated solution of sodium bicarbonate, filtered, washed with H_2O. Then the product was dried under reduced pressure to give the desired ester. ^{1}H NMR (CD_3OD): δ 0.95 (t, 3H, J = 7.35 Hz), 1.33–1.68 (m, 8H), 1.89–2.12 (m, 4H), 2.28–2.42 (m, 2H), 4.08 (t, 2H, J = 6.55 Hz), 6.89 (s, 1H). ESI Mass Spectrum $C_{18}H_{27}N_4O_5S^+$: 411 (M + 1).

[00492] Example 109: 4-[({4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]cyclohexane carboxylic acid (cis isomer)

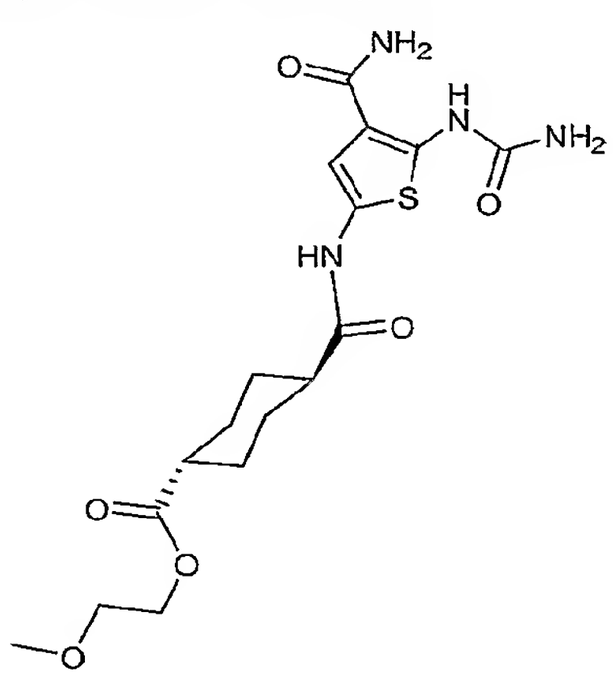
[00493]



[00494] The crude solid salt of 2-[(aminocarbonyl)amino]-5-aminothiophene-3-carboxamide (0.15 g) (prepared according to either Example 2A or Example 2B) was combined with 1.5 mmol of carboxylic acid, HBTU (BF_4) (0.32 g, 1 mmol), N,N-dimethylethylamine (1.6 mL) and DMSO (1.5 mL). The mixture was stirred for 1 hour, then most of the liquids were stripped off. The residue was triturated in 100 mL of CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with water (100 mL) overnight, filtered, washed with 20 mL of ether, and triturated with 5 mL of methanol for 30 minutes. Then the product was filtered and dried under reduced pressure to give a solid. ^{1}H NMR (CD_3OD): δ 1.54–1.82 (m, 6H), 2.10–2.24 (m, 2H), 2.36–2.50 (m, 1H), 2.54–2.64 (m,1H), 6.89 (s, 1H). Mass of molecular ion: 355 (M + 1).

[00495] Example 110: 2-methoxyethyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]cyclohexanecarboxylate

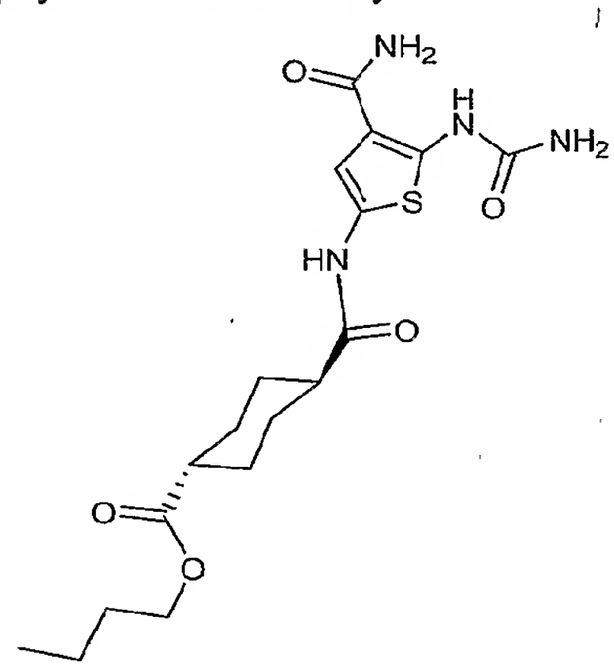
[00496]



[00497] 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]cyclohexanecarboxylic acid (Example 109, 0.12 g, 0.34 mmol) was combined with

2.5 mmol of 2-methoxyethanol, HBTU (BF_4) 0.17 g (0.5 mmol), N,N-dimethylethylamine (0.7 mL), and DMSO (1.0 mL). The mixture was stirred overnight, then most of the liquids were stripped off. The residue was triturated in 100 mL of CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with water (100 mL) overnight, filtered, triturated with 50 mL of a saturated solution of sodium bicarbonate, filtered, washed with water. Then the product was dried under reduced pressure to give the desired ester. ^{1}H NMR (CD_3OD): δ 1.40-1.68 (m, 4H), 1.89-2.08 (m, 2H), 2.10-2.13 (m, 2H), 2.28-2.46 (m, 2H),3.58-3.63 (m, 2H), 4.18-4.24 (m, 2H), 3.40 (s, 3H), 6.89 (s, 1H). Mass of molecular ion: 413 (M + 1).

[00498] Example 110.1: Butyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl] cyclohexanecarboxylate

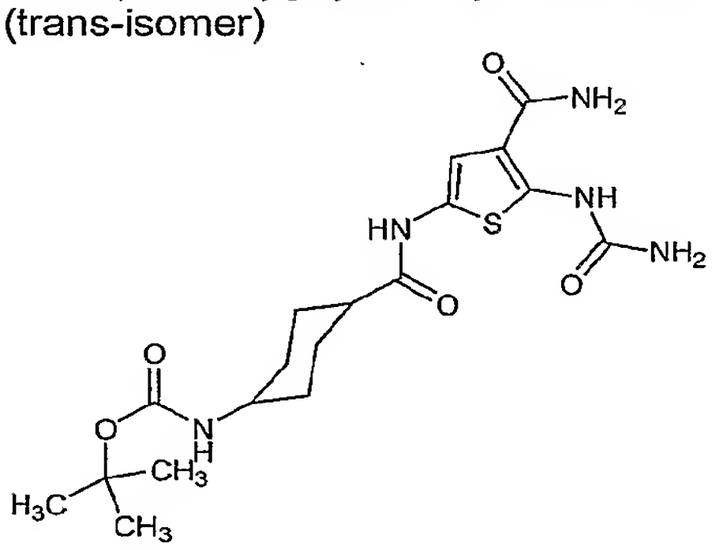


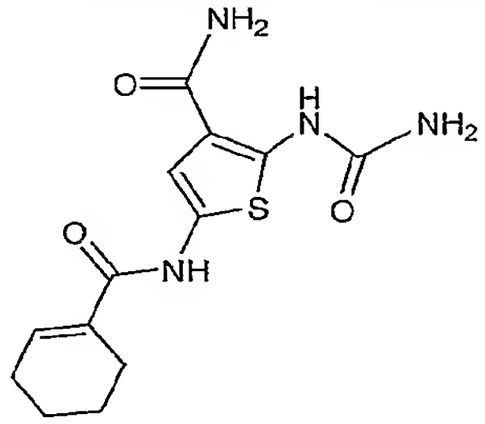
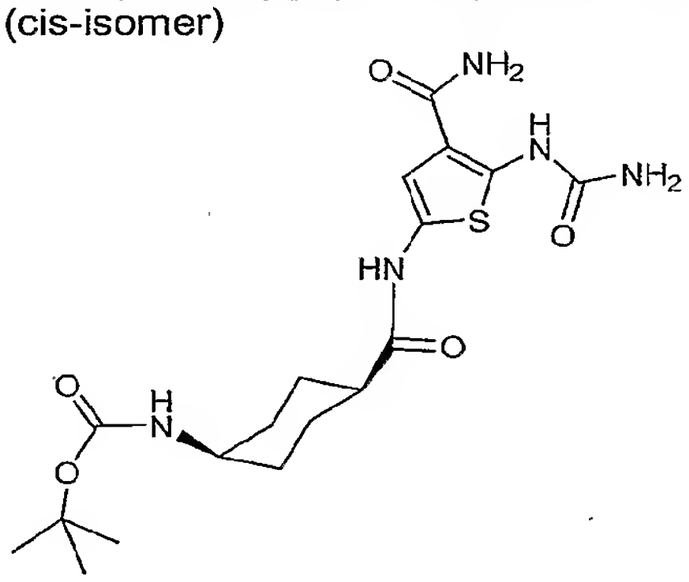
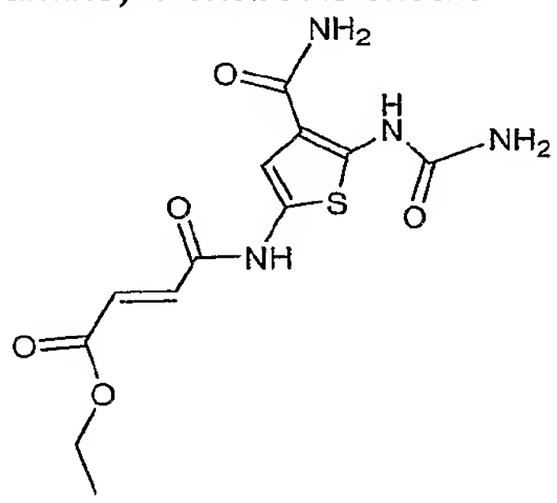
[00499]

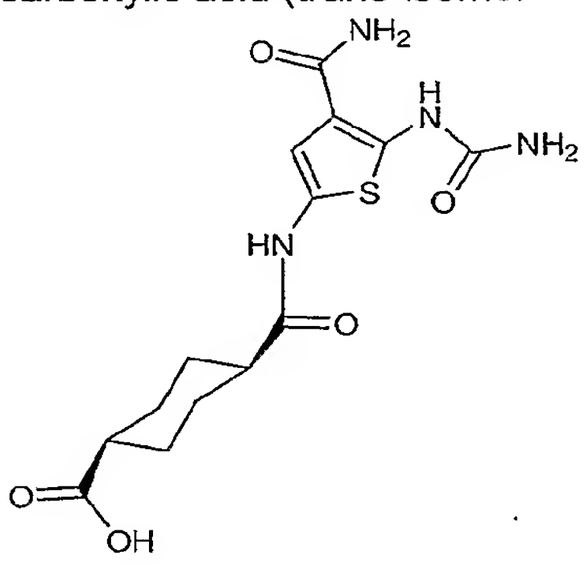
[00500] Prepared analogously to Example 110. ^{1}H NMR (CD_3OD): δ 0.95 (t, 3H, J = 7.35 Hz), 1.33-1.68 (m, 8H), 1.89-2.12 (m, 4H), 2.28-2.42 (m, 2H), 4.08 (t, 2H, J = 6.55 Hz), 6.89 (s, 1H). Mass of molecular ion: 411 (M + 1).

[00501] Examples 111-115, shown in Table IX below, were prepared analogously to Example 109.

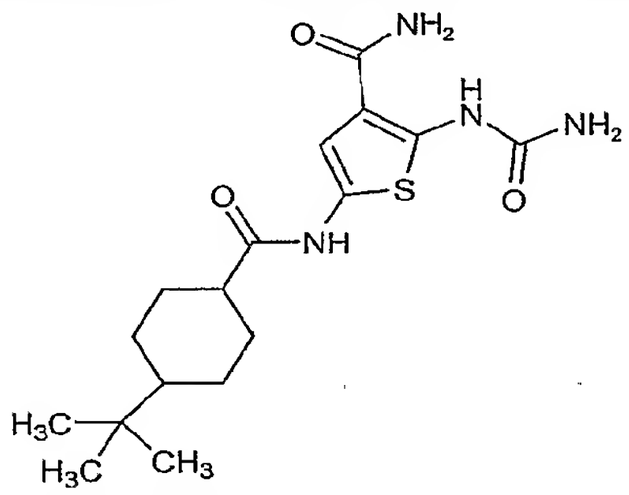
Table IX

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
111	Tert-butyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl} amino)carbonyl] cyclohexyl carbamate (trans-isomer) 	(CD_3OD): δ 1.18-1.35 (m, 3H), 1.42 (s, 9H), 1.46-1.72 (m, 2H), 1.86-2.08 (m, 4H), 2.22-2.36 (m, 1H), 6.79 (s, 1H).	426

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
112	2-[(Aminocarbonyl) amino]-5-[(cyclohex-1-en-1-ylcarbonyl) amino]thiophene-3-carboxamide 	(CD_3OD/d_6-DMSO (4:1)): δ 1.21-1.65 (m, 4H), 2.03-2.28 (m, 4H), 6.59-62 (m, 1H), 6.72 (s, 1H).	309
113	Tert-butyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl} amino)carbonyl] cyclohexylcarbamate (cis-isomer) 	(CD_3OD): δ 1.48 (s, 9H), 1.52-1.95 (m, 8H), 2.38-2.51 (m, 1H), 3.58-3.73 (s, 1H), 6.79 (s, 1H).	426
114	Ethyl (2E)-4-({4-(aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl} amino)-4-oxobut-2-enoate 	(CD_3OD/d_6-DMSO(4:1)): δ 1.31 (t, 3H, J = 7.04 Hz), 4.27 (q, 2H, J = 6.98 Hz), 6.82 (d, 1H, J = 15.5 Hz), 6.87 (s, 1H), 7.12 (d, 1H, J = 15.3 Hz).	327

Example	Name and Structure	^{1}H NMR	MS(ES$^+$) (M+1)
115	4-[({4-(Aminocarbonyl)-5-[(aminocarbonyl) amino]thien-2-yl} amino)carbonyl] cyclohexane carboxylic acid (trans-isomer 	(CD_3OD): δ 1.39–1.69 (m, 4H), 1.90–2.12 (m, 4H), 2.22–2.44 (m, 2H), 6.90 (s, 1H).	355

[00502] Example 116: 2-[(aminocarbonyl)amino]-5-{[(4-tert-butylcyclohexyl)carbonyl]amino}thiophene-3-carboxamide



[00503]

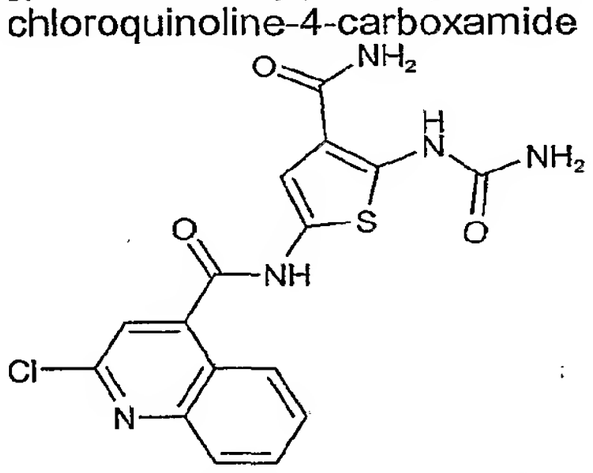
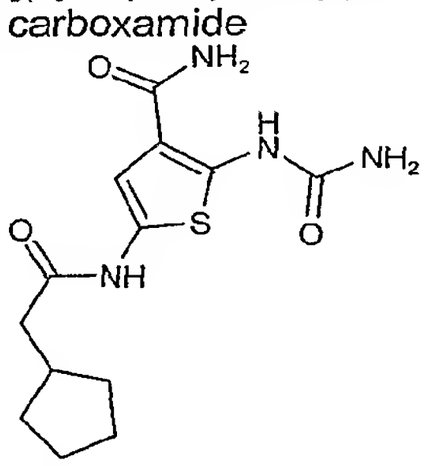
[00504] To 4-tert-butylcyclohexane carboxylic acid (0.064 g, 0.348 mmol) in a 2 dram vial was added 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.127 g, 0.333 mmol), 5-amino-2-[(aminocarbonyl)amino]thiophene-3-carboxamide hydrochloride (0.050 g, 0.211 mmol), 4-methylmorpholine (0.232 mL, 2.110 mmol), and 1.0 mL of DMSO. The reaction mixture was stirred overnight at room temperature and the reaction progress was monitored by HPLC. Volatiles were removed via nitrogen stream and the crude reaction mixture was purified by reverse phase chromatography. Concentration of the desired fractions afforded an orange solid. ^{1}H NMR (d^6-DMSO, 400 MHz) (mixture of cis and trans isomers) δ 0.79 (s, 9H, minor isomer), 0.82 (s, 9H, major isomer), 0.94 (m, 2H), 1.21-1.52 (m, 3H), 1.80 (m, 2H), 2.02 (d, 1H, J = 12.4 Hz, minor isomer), 2.21 (t, 1H, J = 12.0 Hz, major isomer), 6.71 (m, 3H), 7.08 (brs, 1H), 7.51 (brs, 1H), 10.43 (s, 1H, minor isomer), 10.54 (s, 1H, major isomer), 10.77 (m, 1H); MS (ES+) 367 (M+1); HRMS (ES+) *m/z* calc'd for ($C_{17}H_{26}N_4O_3S$) 367.1798, found 367.1778; LC (min) 2.810 (100%).

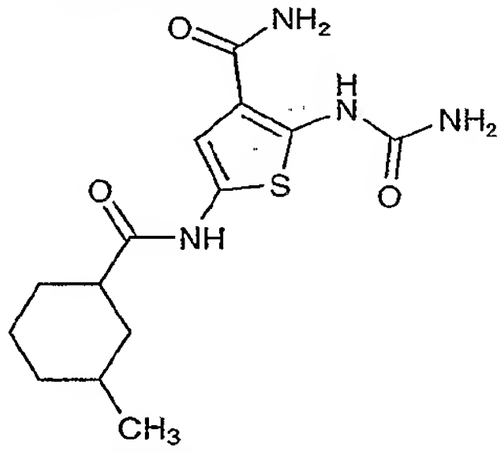
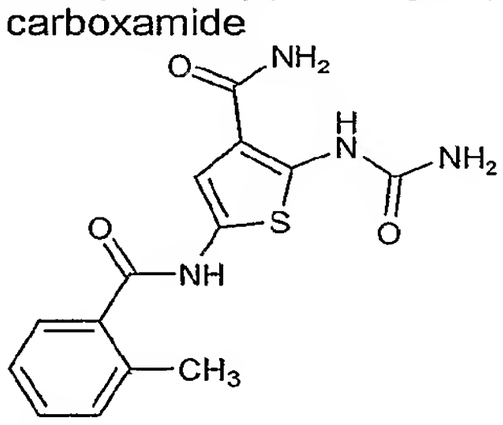
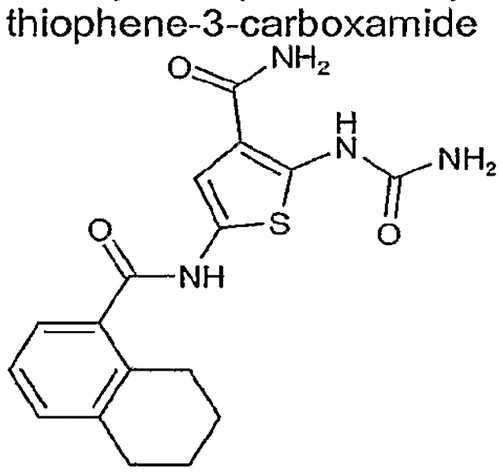
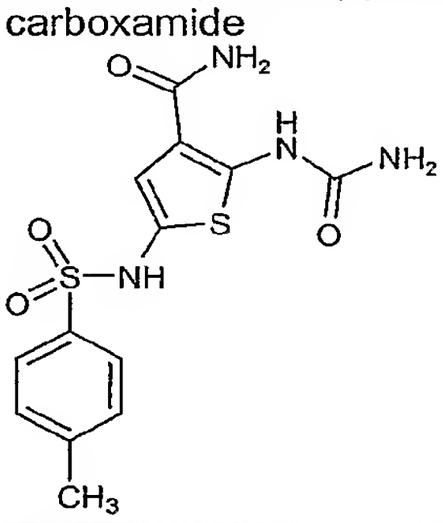
[00505] Examples 117-212 are reported in Table X. Examples 117-193 were prepared via parallel synthesis analogously to the procedure of Example 116. Examples 194-212 were prepared via parallel synthesis analogously to Example 116 with the following exceptions: To 0.402 mmol of corresponding acid was added 0.152 g (0.401 mmol) of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, 0.100 g (0.423 mmol) of 5-amino-2-

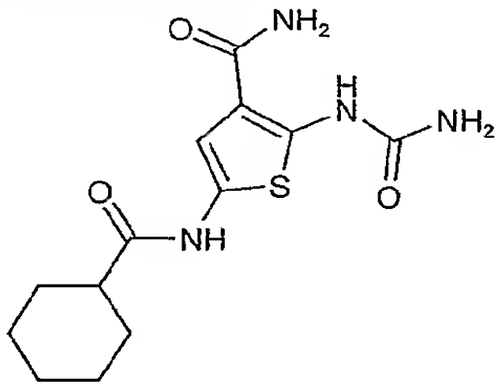
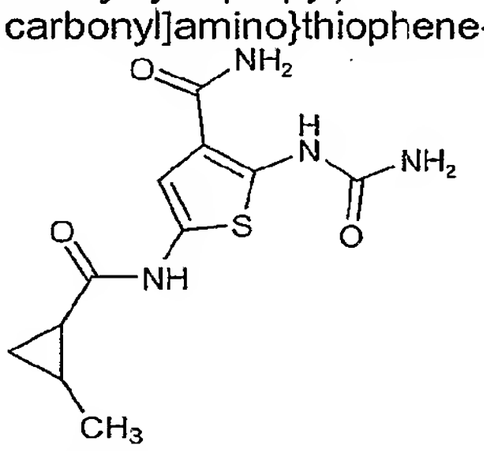
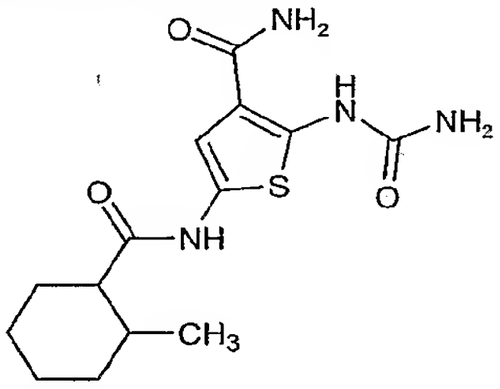
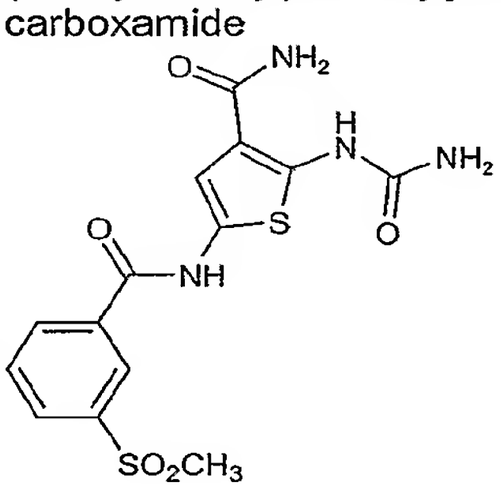
[(aminocarbonyl)amino]thiophene-3-carboxamide hydrochloride, 0.465 mL (4.230 mmol) 4-methylmorpholine, and 1.5 mL DMSO.

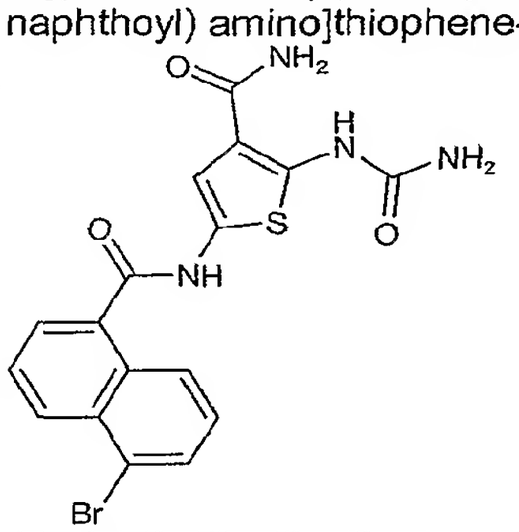
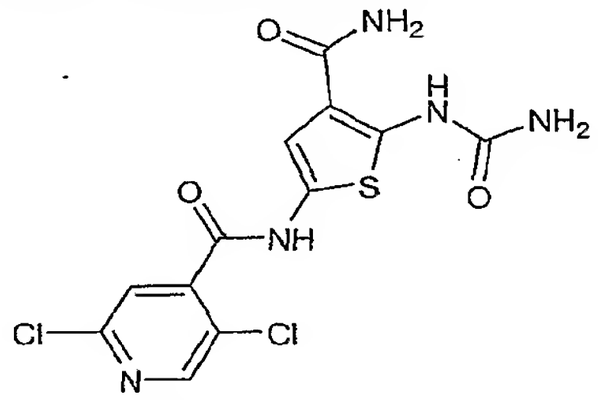
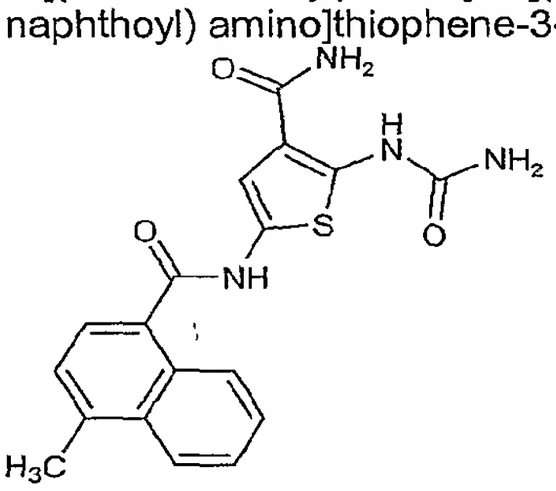
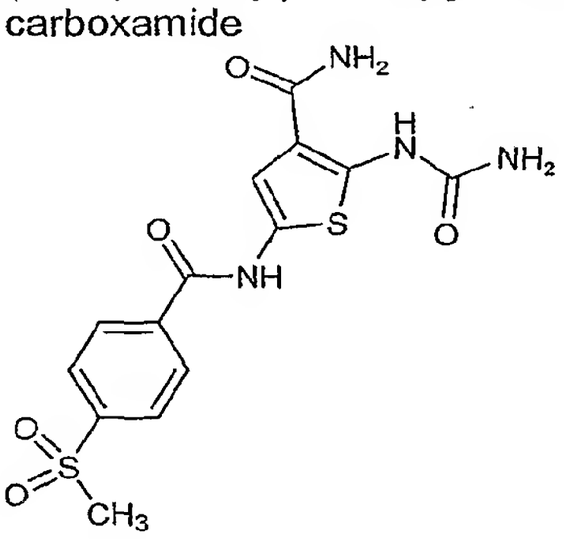
[00506] The parallel synthesis apparatus consisted of an aluminum block (obtained from J-KEM Scientific, Inc., St. Louis, MO, USA or ChemGlass Inc., Vineland, NJ, USA), which can be heated or cooled to the appropriate temperature, with a set of wells for 20–50 mL glass vessels. The parallel reactor blocks can be used under reflux conditions and inert atmosphere. The HPLC retention time was determined using analytical LCMS reverse phase analysis and represents the time obtained for the compound having the desired molecular ion. The retention time is based on the observed time in the UV chromatogram. The molecular ion listed in Table X is the baseline (100%) peak, unless otherwise noted. Analytical LCMS reverse phase chromatography was carried out using a C18 column 2.1 mm i.d. x 30 mm and a linear gradient of 5% acetonitrile in 0.1% TFA/water to 95% acetonitrile in 0.1% TFA/water over 4.5 min. at a flow rate of 1 mL/min. The eluant composition was held at 95% acetonitrile in 0.1% TFA/water from 4.5 min to 6 min. The LCMS was equipped with a diode array detector, a mass spectral detector (MSD) and an evaporative light scattering detector (ELS). A flow splitter was attached after the UV diode array detector to allow flow to the MSD and ELS. Mass spectra were obtained using an Agilent MSD in electrospray positive mode. Preparative reverse phase chromatography was carried out using a C18 column 41.4 mm i.d. of 50 mm, 100 mm or 300 mm length.

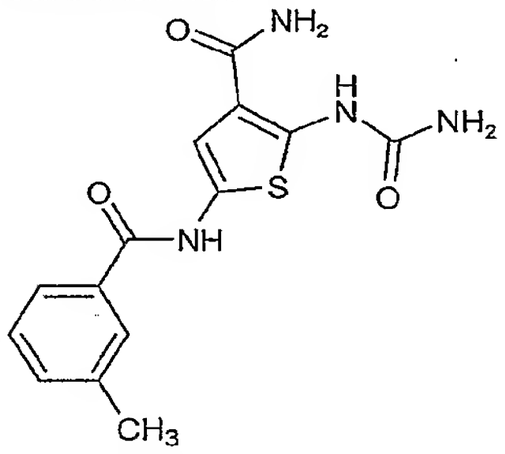
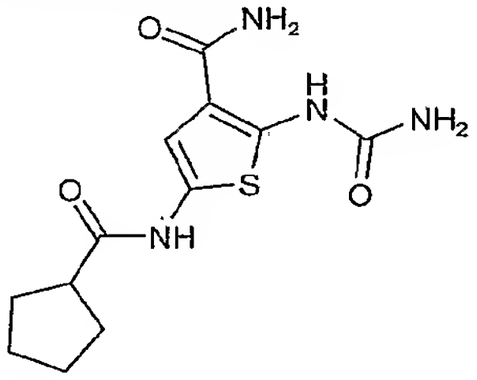
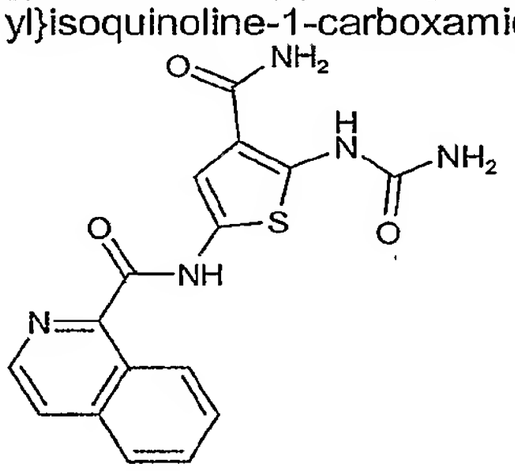
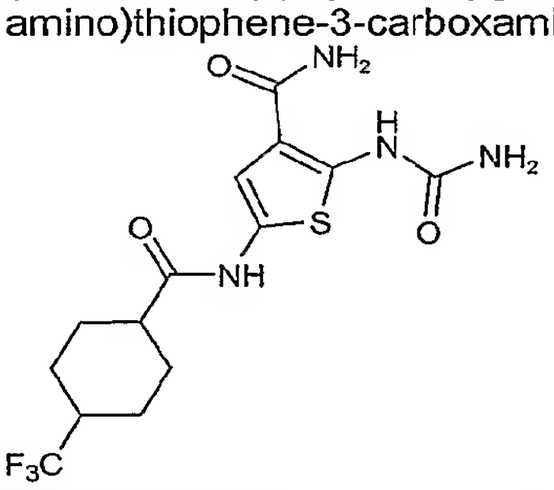
Table X

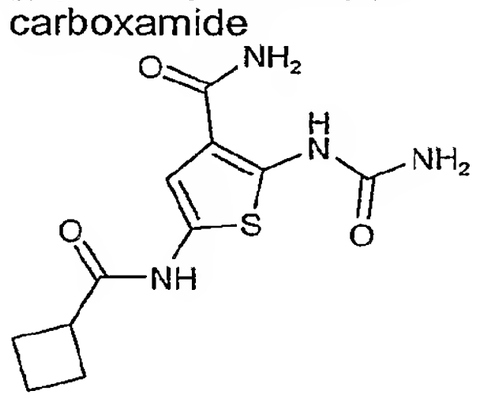
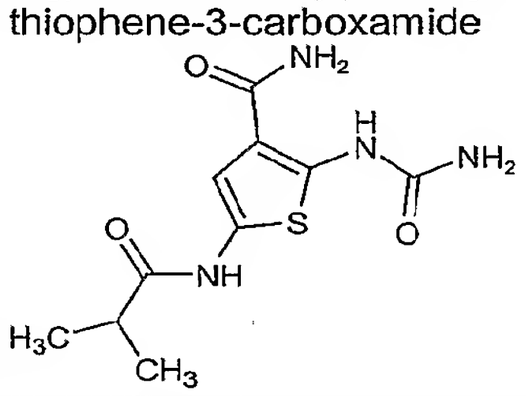
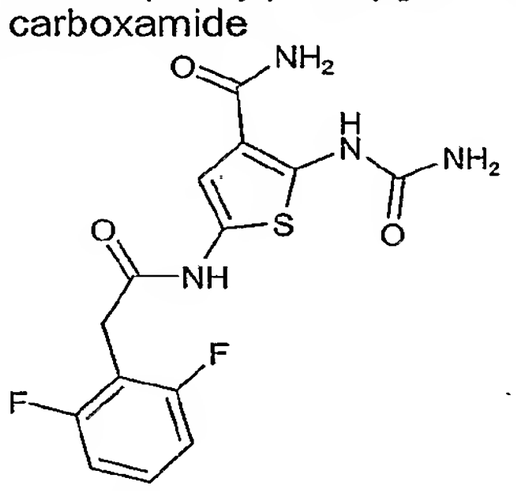
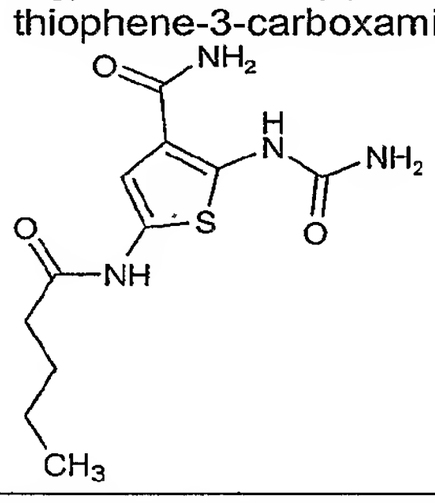
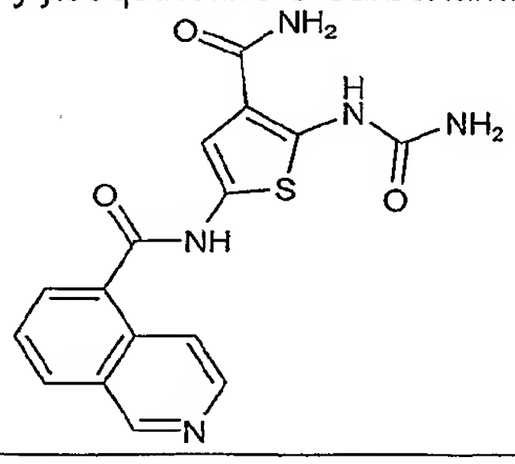
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
117	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-2-chloroquinoline-4-carboxamide 	2.126	390.0	390.0459
118	2-[(aminocarbonyl)amino]-5-[(cyclopentylacetyl) amino]thiophene-3-carboxamide 	2.009	311.1	311.1201

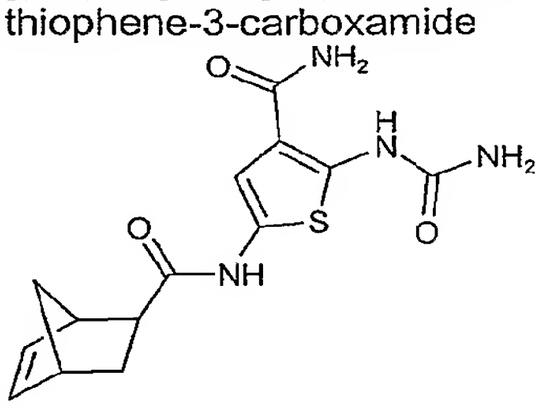
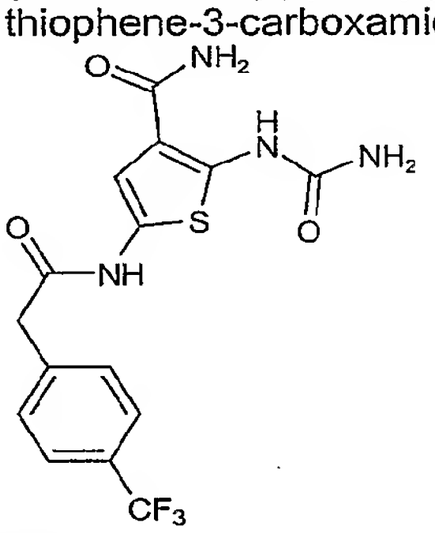
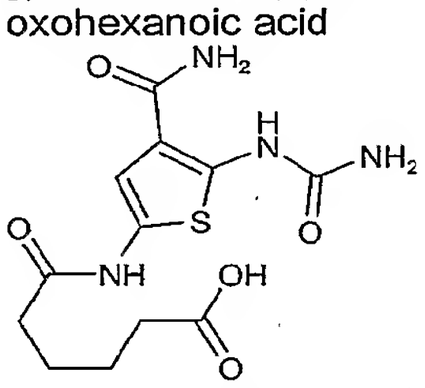
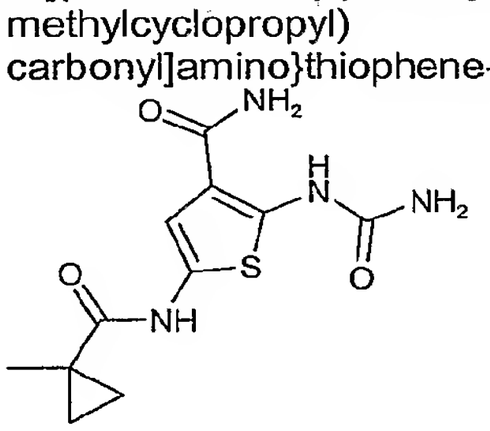
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
119	2-[(aminocarbonyl)amino]-5-{[(3-methylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	2.228	325.1	325.1291
120	2-[(aminocarbonyl)amino]-5-[(2-methylbenzoyl) amino]thiophene-3-carboxamide 	1.910	319.1	319.0880
121	2-[(aminocarbonyl)amino]-5-[(5,6,7,8-tetrahydronaphthalen-1-yl-carbonyl)amino] thiophene-3-carboxamide 	2.324	359.1	359.1134
122	2-[(aminocarbonyl)amino]-5-{[(4-{[(4-methylphenyl) sulfonyl]amino} cyclohexyl)carbonyl] amino}thiophene-3-carboxamide 	2.202	480.1	480.1363

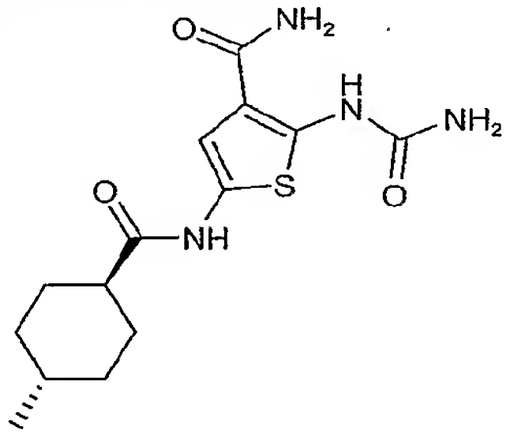
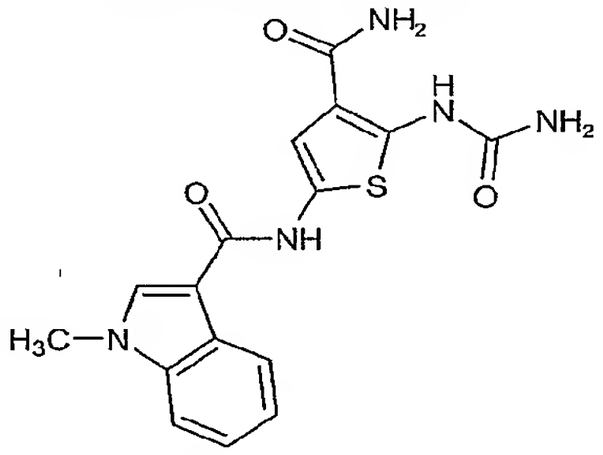
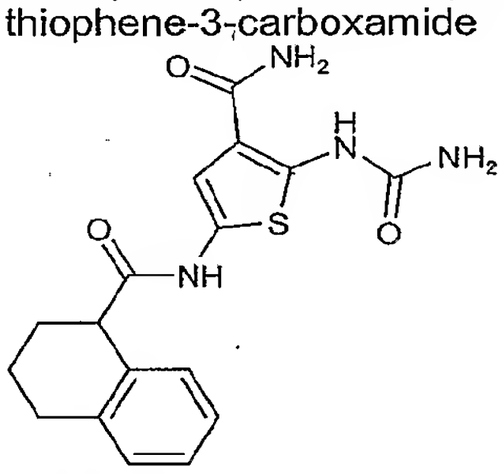
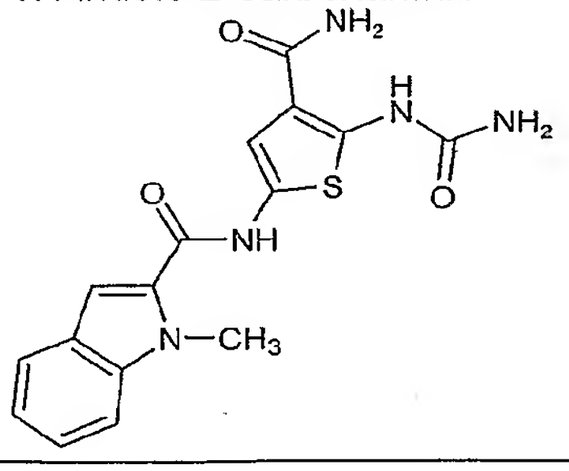
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
123	2-[(aminocarbonyl)amino]-5-[(cyclohexylcarbonyl) amino]thiophene-3-carboxamide 	1.940	311.1	311.1173
124	2-[(aminocarbonyl)amino]-5-{[(2-methylcyclopropyl) carbonyl]amino}thiophene-3-carboxamide 	1.510	283.1	283.0839
125	2-[(aminocarbonyl)amino]-5-{[(2-methylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	2.200	325.1	325.1290
126	2-[(aminocarbonyl)amino]-5-{[3-(methylsulfonyl) benzoyl]amino}thiophene-3-carboxamide 	1.616	383.1	383.0483

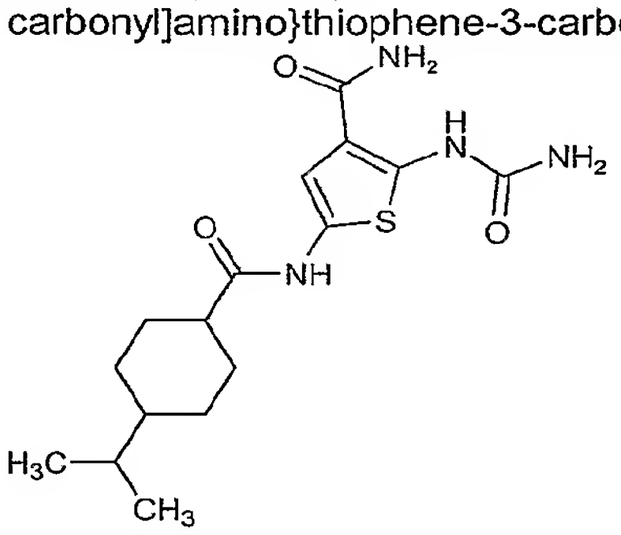
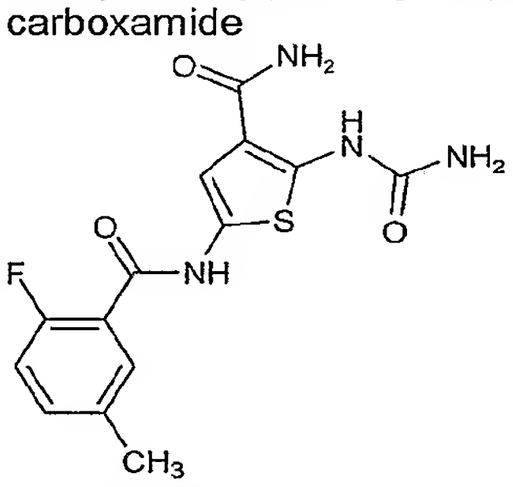
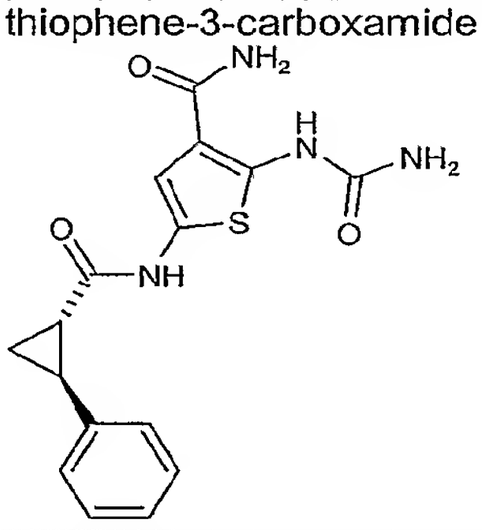
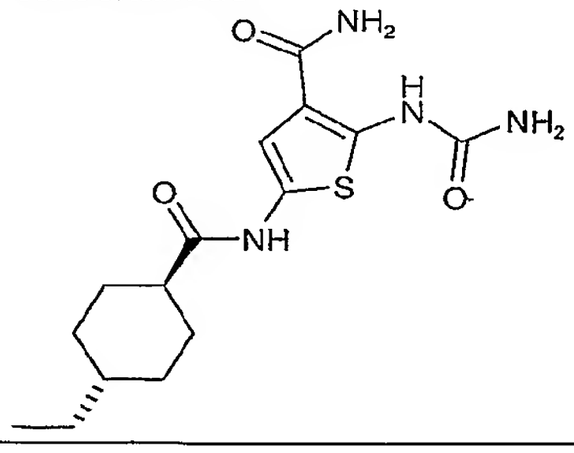
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
127	2-[(aminocarbonyl)amino]-5-[(5-bromo-1-naphthoyl) amino]thiophene-3-carboxamide 	2.536	433.0	433.0008
128	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-2,5-dichloroisonicotinamide 	1.806	374.0	373.9845
129	2-[(aminocarbonyl)amino]-5-[(4-methyl-1-naphthoyl) amino]thiophene-3-carboxamide 	2.358	369.1	369.1031
130	2-[(aminocarbonyl)amino]-5-{[4-(methylsulfonyl) benzoyl]amino}thiophene-3-carboxamide 	1.593	383.1	383.0478

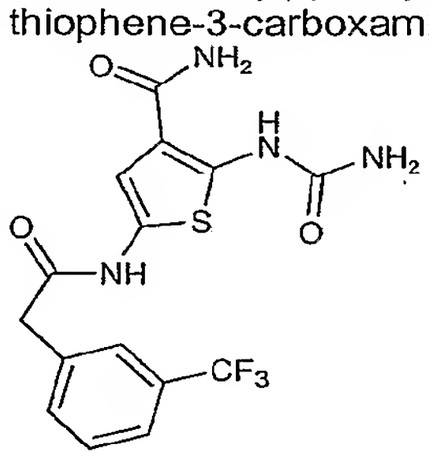
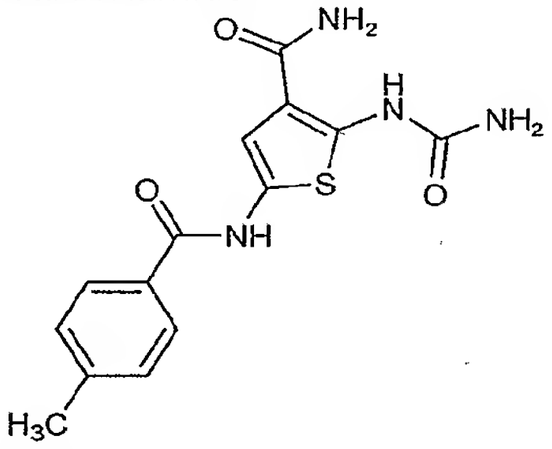
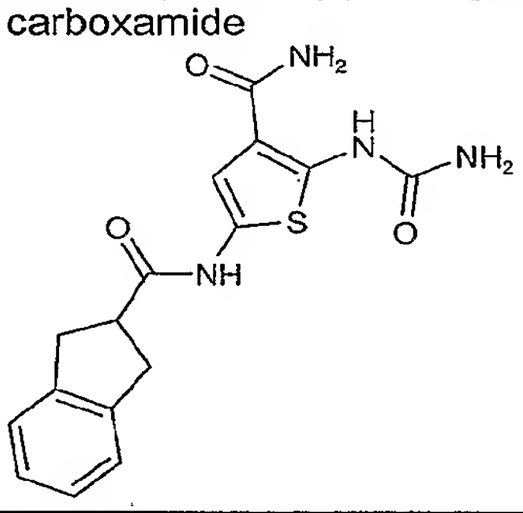
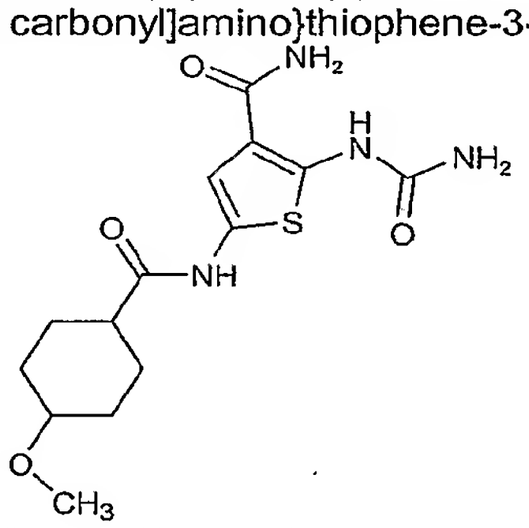
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
131	2-[(aminocarbonyl)amino]-5-[(3-methylbenzoyl) amino]thiophene-3-carboxamide 	2.018	319.1	319.0845
132	2-[(aminocarbonyl)amino]-5-[(cyclopentylcarbonyl) amino]thiophene-3-carboxamide 	1.729	297.1	297.0990
133	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}isoquinoline-1-carboxamide 	2.121	356.1	356.0814
134	2-[(aminocarbonyl)amino]-5-({[4-(trifluoromethyl) cyclohexyl]carbonyl} amino)thiophene-3-carboxamide 	2.242	379.1	379.1019

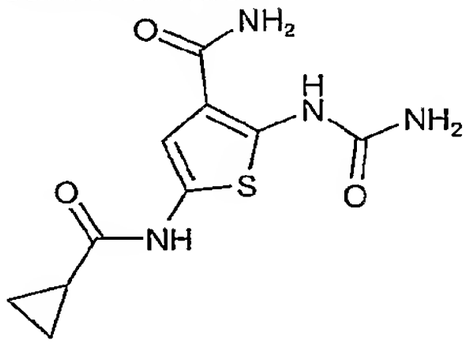
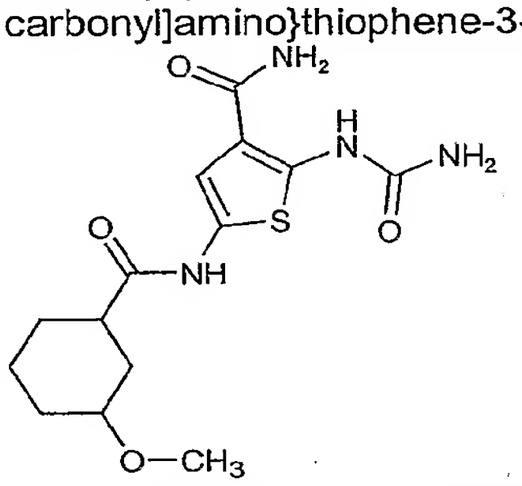
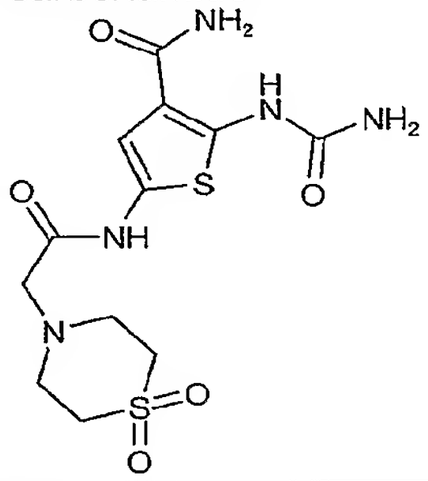
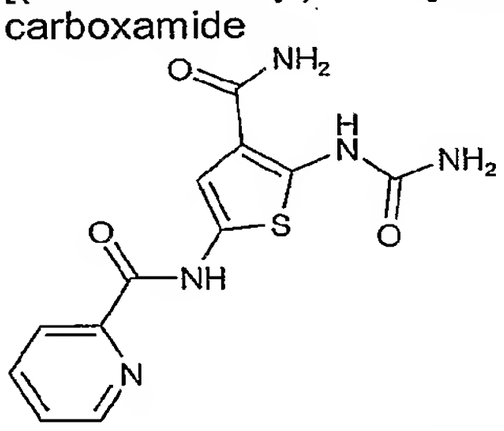
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
135	2-[(aminocarbonyl)amino]-5-[(cyclobutylcarbonyl) amino]thiophene-3-carboxamide 	1.440	283.1	283.0817
136	2-[(aminocarbonyl)amino]-5-(isobutyrylamino) thiophene-3-carboxamide 	1.008	271.1	271.0080
137	2-[(aminocarbonyl)amino]-5-{[(2,6-difluorophenyl) acetyl]amino}thiophene-3-carboxamide 	1.896	355.1	355.0680
138	2-[(aminocarbonyl)amino]-5-(butyrylamino) thiophene-3-carboxamide 	1.182	271.1	271.0882
139	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}isoquinoline-5-carboxamide 	0.818	356.1	356.0819

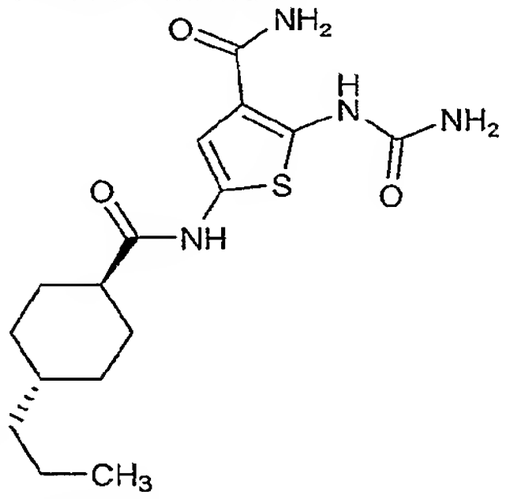
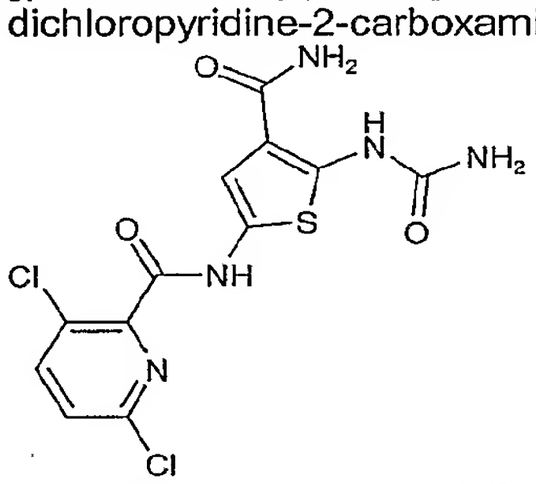
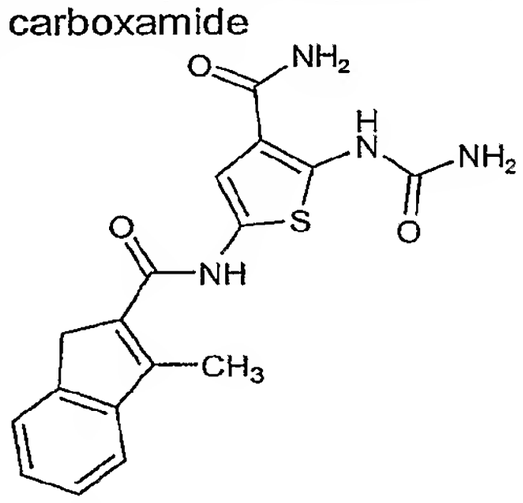
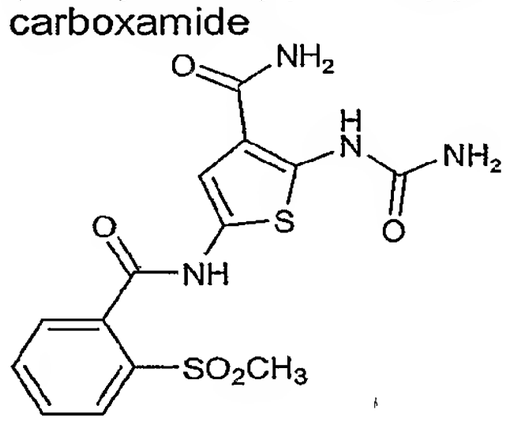
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
140	2-[(aminocarbonyl)amino]-5-[(bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)amino] thiophene-3-carboxamide 	1.821	321.1	321.0992
141	2-[(aminocarbonyl)amino]-5-({[4-(trifluoromethyl) phenyl]acetyl}amino) thiophene-3-carboxamide 	2.369	387.1	387.0707
142	6-({4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}amino)-6-oxohexanoic acid 	0.838	329.1	329.0933
143	2-[(aminocarbonyl)amino]-5-{[(1-methylcyclopropyl) carbonyl]amino}thiophene-3-carboxamide 	1.483	283.1	283.0843

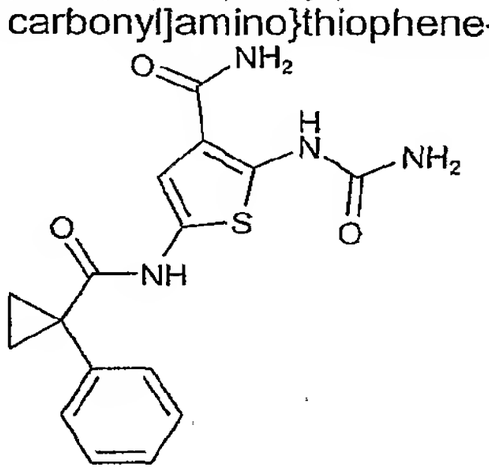
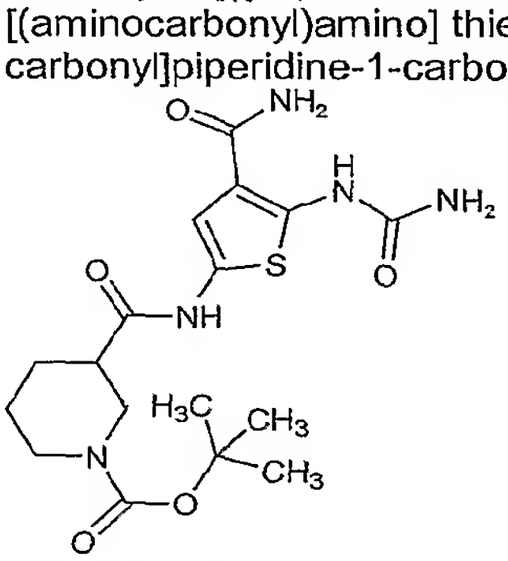
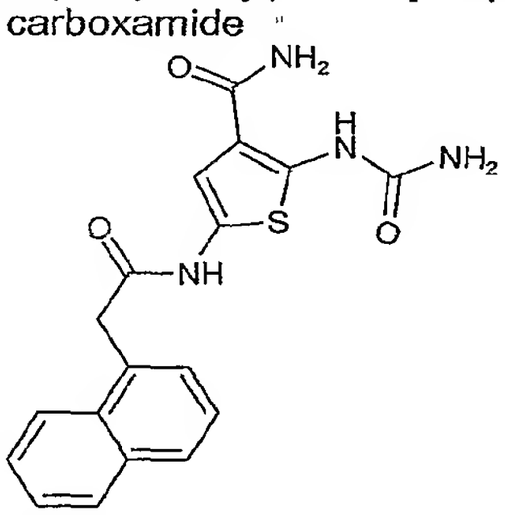
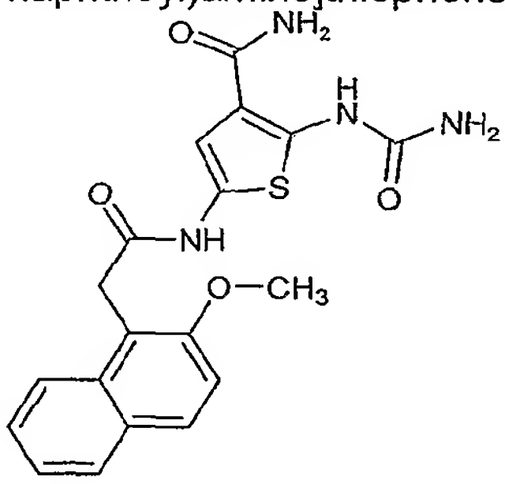
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
144	2-[(aminocarbonyl)amino]-5-{[(4-methylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	2.243	325.1	325.1350
145	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-1-methyl-1H-indole-3-carboxamide 	2.088	358.1	358.0957
146	2-[(aminocarbonyl)amino]-5-[(1,2,3,4-tetrahydronaphthalen-1-ylcarbonyl)amino] thiophene-3-carboxamide 	2.224	359.1	359.1171
147	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-1-methyl-1H-indole-2-carboxamide 	2.323	358.1	358.0948

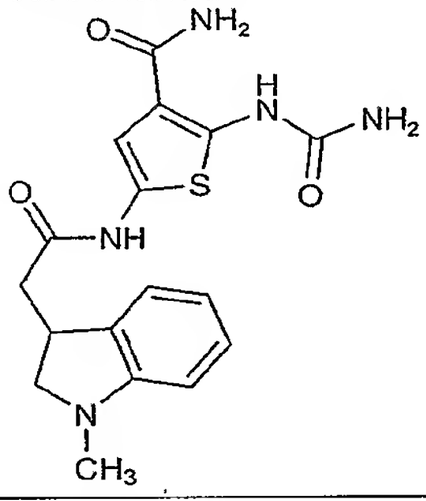
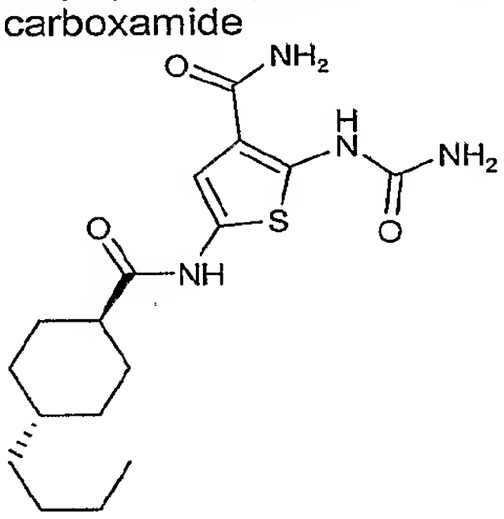
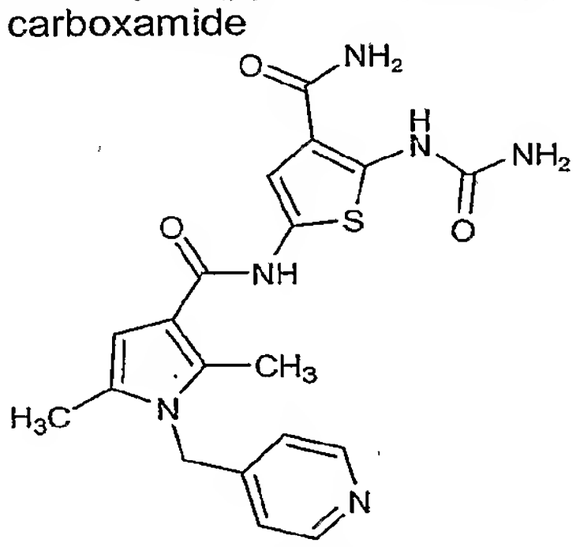
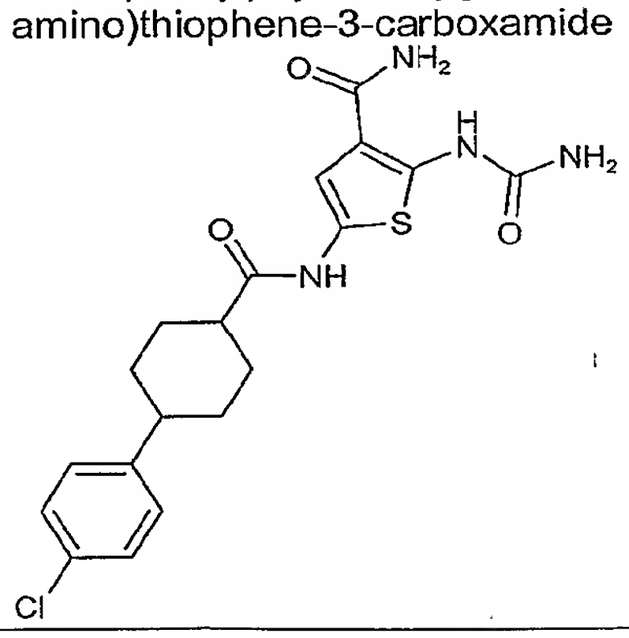
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
148	2-[(aminocarbonyl)amino]-5-{[(4-isopropylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	2.650	353.2	353.1658
149	2-[(aminocarbonyl)amino]-5-[(2-fluoro-5-methylbenzoyl)amino] thiophene-3-carboxamide 	2.009	337.1	337.0738
150	2-[(aminocarbonyl)amino]-5-({[(1S,2S)-2-phenylcyclopropyl] carbonyl}amino) thiophene-3-carboxamide 	2.211	345.1	345.1029
151	2-[(aminocarbonyl)amino]-5-{[(4-ethylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	2.498	339.1	339.1472

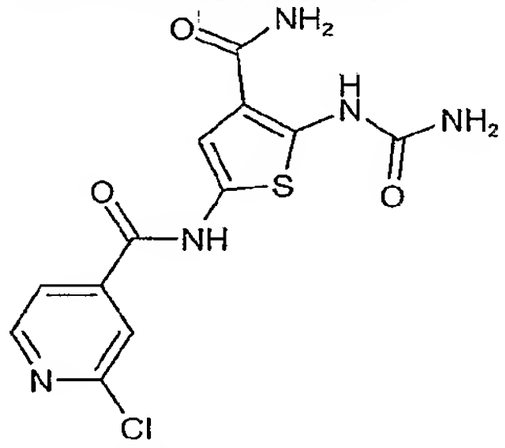
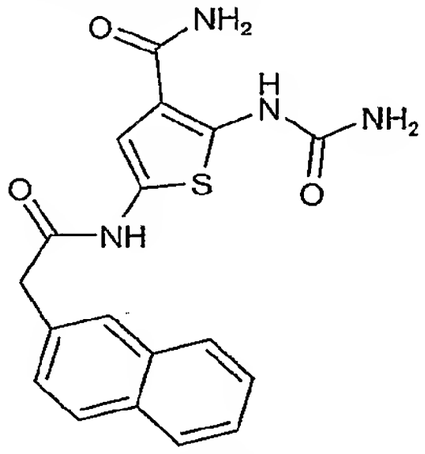
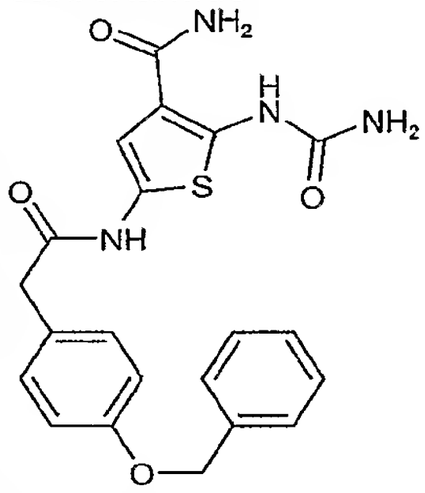
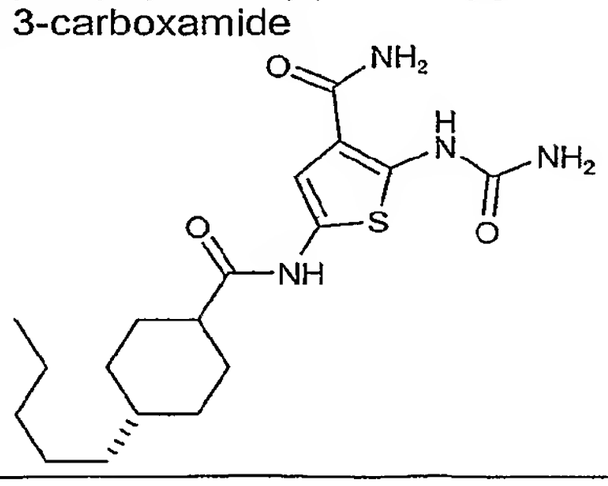
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
152	2-[(aminocarbonyl)amino]-5-({[3-(trifluoromethyl) phenyl]acetyl}amino) thiophene-3-carboxamide 	2.349	387.1	387.0697
153	2-[(aminocarbonyl)amino]-5-[(4-methylbenzoyl) amino]thiophene-3-carboxamide 	2.010	319.1	319.0860
154	2-[(aminocarbonyl)amino]-5-[(2,3-dihydro-1H-inden-2-ylcarbonyl)amino] thiophene-3-carboxamide 	2.130	345.1	345.1047
155	2-[(aminocarbonyl)amino]-5-{[(4-methoxycyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	1.699	341.1	341.1258

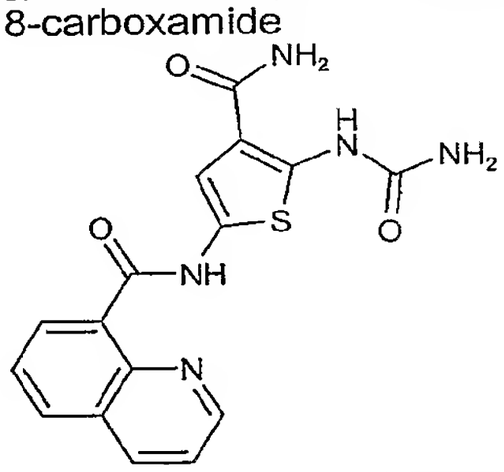
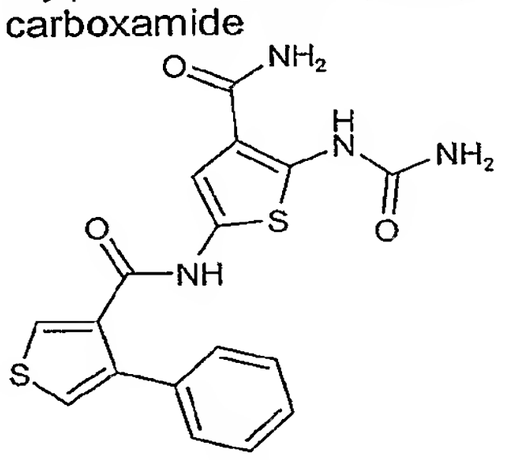
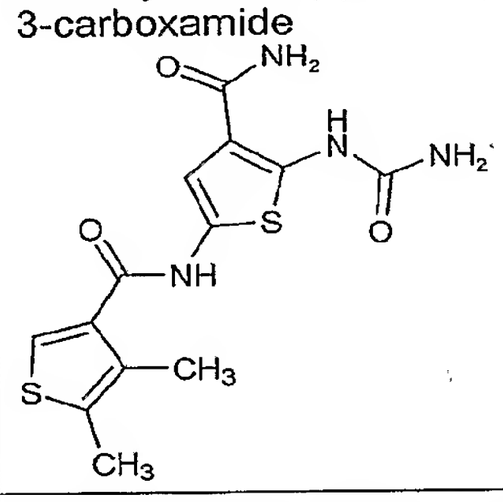
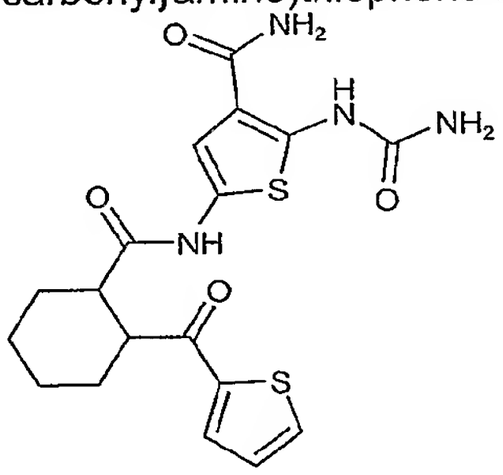
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
156	2-[(aminocarbonyl)amino]-5-[(cyclopropylcarbonyl) amino]thiophene-3-carboxamide 	0.722	269.1	269.0673
157	2-[(aminocarbonyl)amino]-5-{[(3-methoxycyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	1.684	341.1	341.1231
158	2-[(aminocarbonyl)amino]-5-({4-[(1,1-dioxidothiomorpholin-4-yl)methyl]benzoyl}amino) thiophene-3-carboxamide 	1.390	452.1	452.1082
159	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}pyridine-2-carboxamide 	1.562	306.1	306.0612

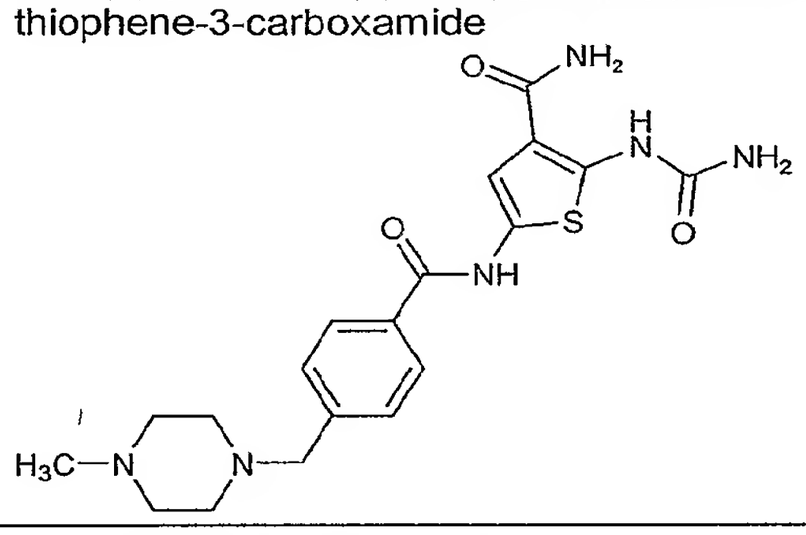
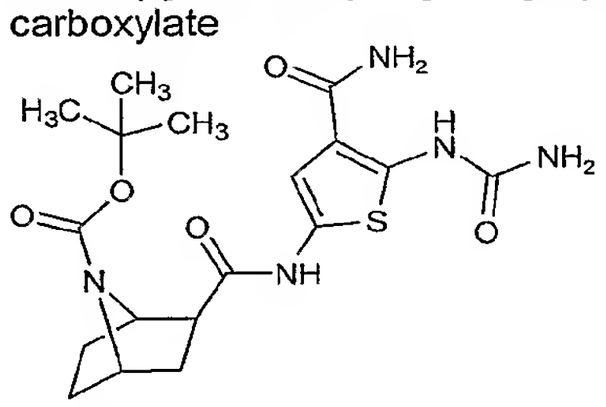
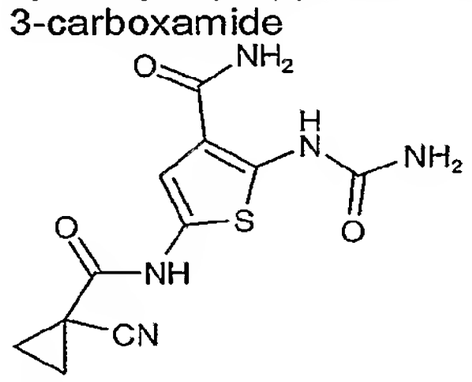
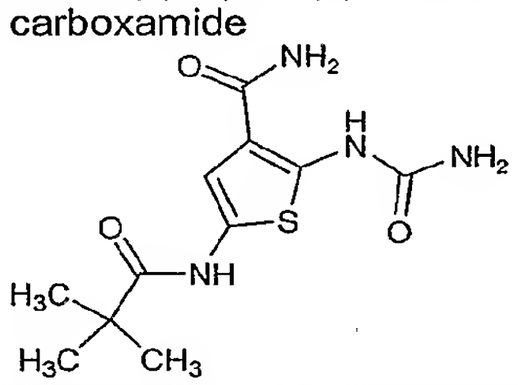
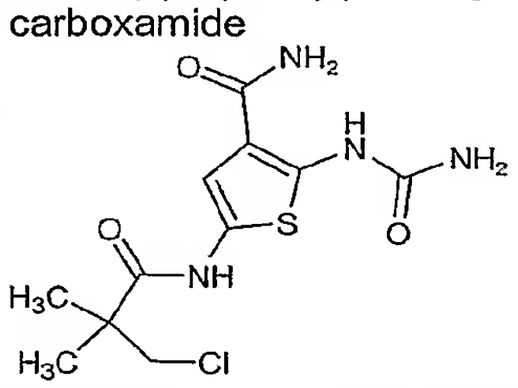
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
160	2-[(aminocarbonyl)amino]-5-{[(4-propylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	2.741	353.2	353.1622
161	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-3,6-dichloropyridine-2-carboxamide 	1.919	374.0	373.9843
162	2-[(aminocarbonyl)amino]-5-{[(3-methyl-1H-inden-2-yl)carbonyl]amino} thiophene-3-carboxamide 	2.334	357.1	357.0968
163	2-[(aminocarbonyl)amino]-5-{[2-(methylsulfonyl) benzoyl]amino}thiophene-3-carboxamide 	1.371	383.1	383.0483

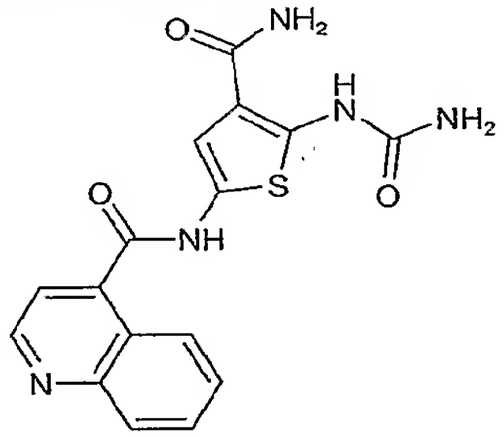
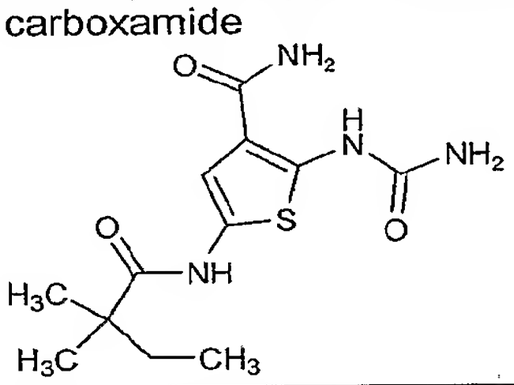
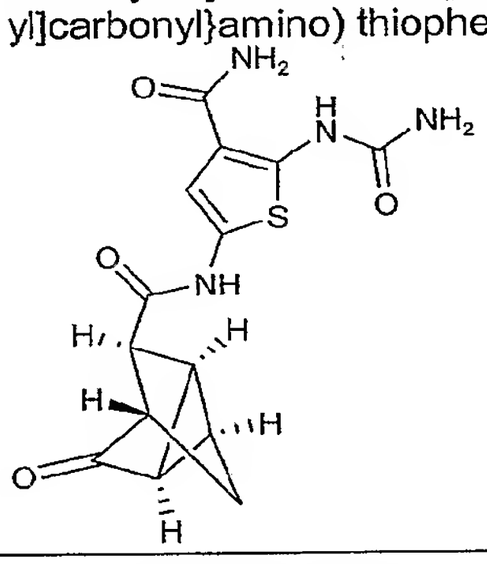
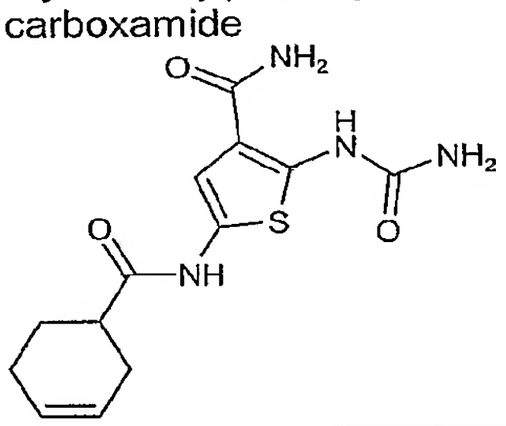
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
164	2-[(aminocarbonyl)amino]-5-{[(1-phenylcyclopropyl) carbonyl]amino}thiophene-3-carboxamide 	2.186	345.1	345.1007
165	tert-butyl 3-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}amino) carbonyl]piperidine-1-carboxylate 	2.278	434.2 M+Na	412.1686
166	2-[(aminocarbonyl)amino]-5-[(1-naphthylacetyl) amino]thiophene-3-carboxamide 	2.301	369.1	369.1033
167	2-[(aminocarbonyl)amino]-5-[(2-methoxy-1-naphthoyl)amino]thiophene-3-carboxamide 	2.125	385.1	385.0950

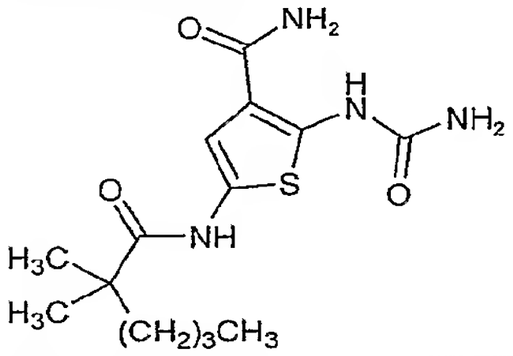
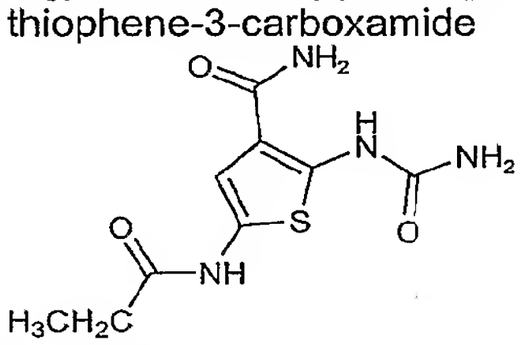
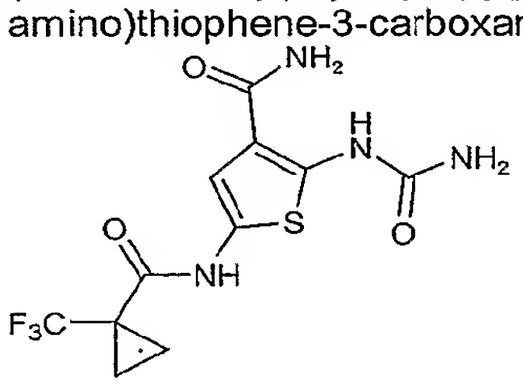
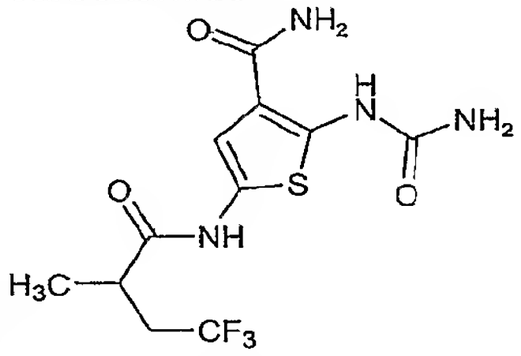
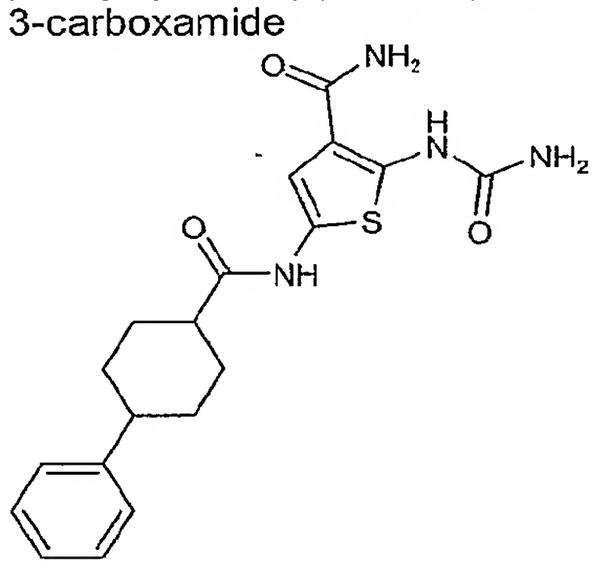
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
168	2-[(aminocarbonyl)amino]-5-{[(1-methyl-1H-indol-3-yl)acetyl]amino} thiophene-3-carboxamide 	2.179	372.1	372.1150
169	2-[(aminocarbonyl)amino]-5-{[(4-butylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	2.961	367.2	367.1772
170	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-2,5-dimethyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxamide 	1.432	413.1	413.1398
171	2-[(aminocarbonyl)amino]-5-({[4-(4-chlorophenyl) cyclohexyl]carbonyl} amino)thiophene-3-carboxamide 	2.845	421.1	421.1059

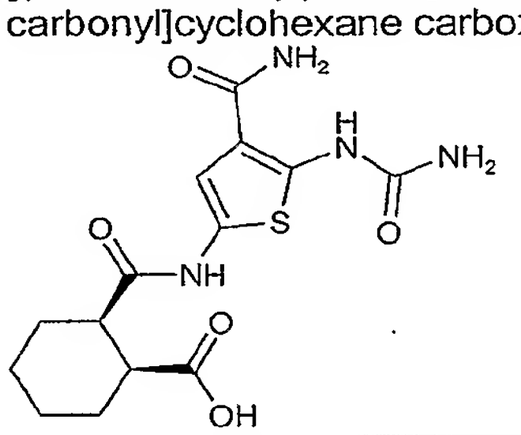
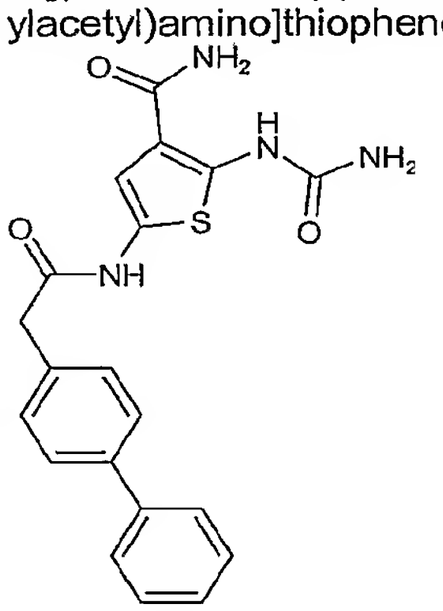
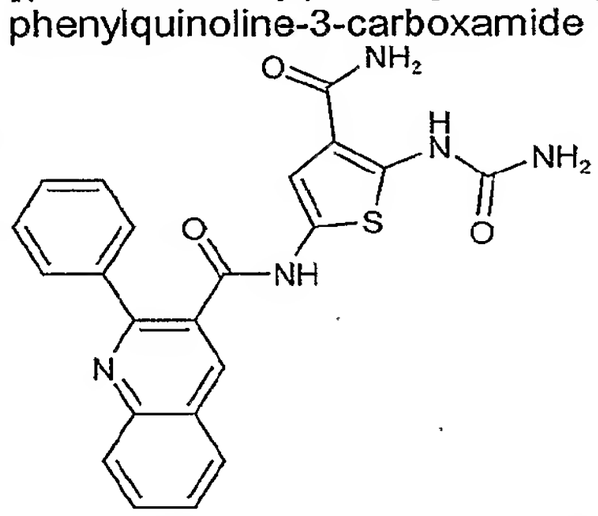
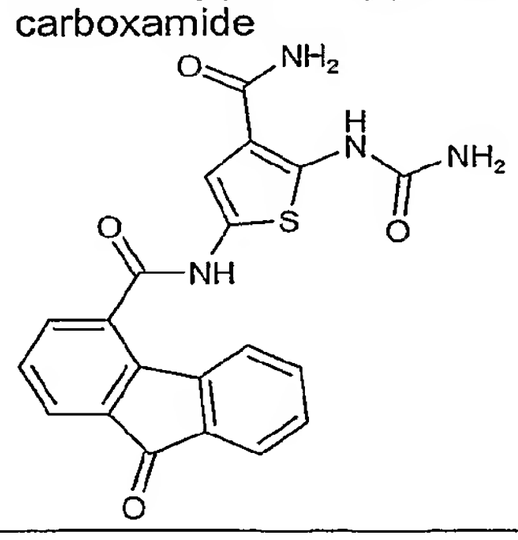
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
172	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-2-chloroisonicotinamide 	1.721	340.0	340.0293
173	2-[(aminocarbonyl)amino]-5-[(2-naphthylacetyl) amino]thiophene-3-carboxamide 	2.339	369.1	369.1014
174	2-[(aminocarbonyl)amino]-5-({[4-(benzyloxy)phenyl] acetyl}amino)thiophene-3-carboxamide 	2.631	425.1	425.1243
175	2-[(aminocarbonyl)amino]-5-{[(4-pentylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	3.180	381.2	381.1945

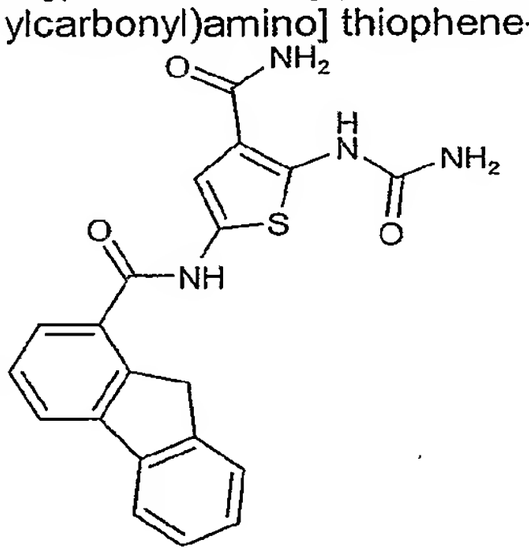
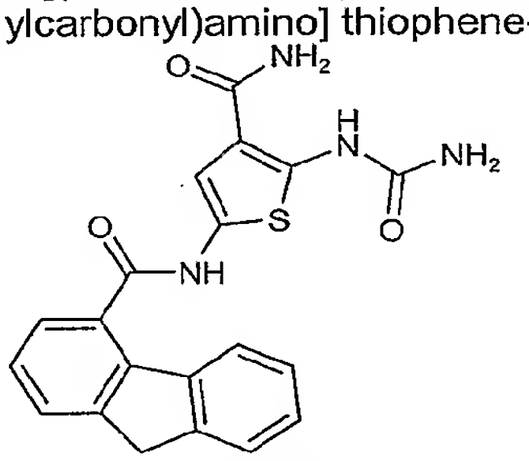
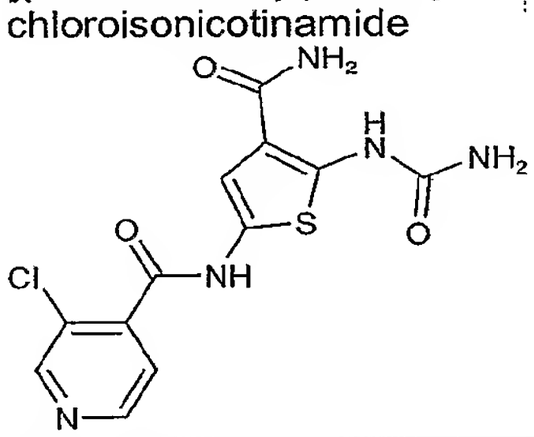
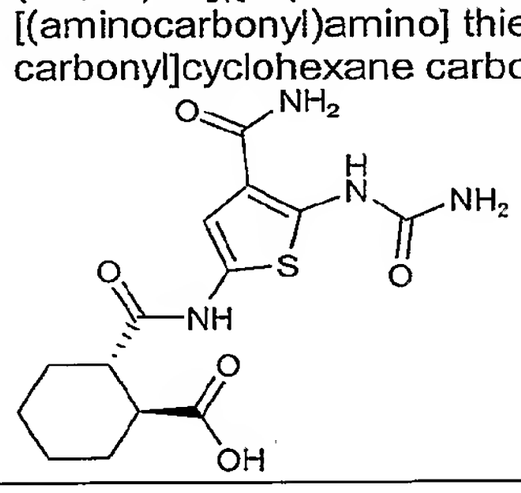
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
176	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}quinoline-8-carboxamide 	1.859	356.1	356.0826
177	2-[(aminocarbonyl)amino]-5-{[(4-phenylthien-3-yl)carbonyl]amino} thiophene-3-carboxamide 	2.268	387.1	387.0562
178	2-[(aminocarbonyl)amino]-5-{[(4,5-dimethylthien-3-yl)carbonyl]amino} thiophene-3-carboxamide 	2.116	339.1	339.0543
179	2-[(aminocarbonyl)amino]-5-({[(1R,2S)-2-(thien-2-ylcarbonyl)cyclohexyl] carbonyl}amino)thiophene-3-carboxamide 	2.292	421.1	421.0965

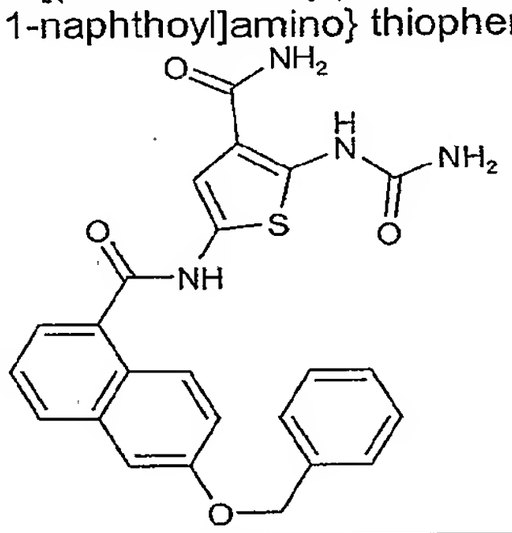
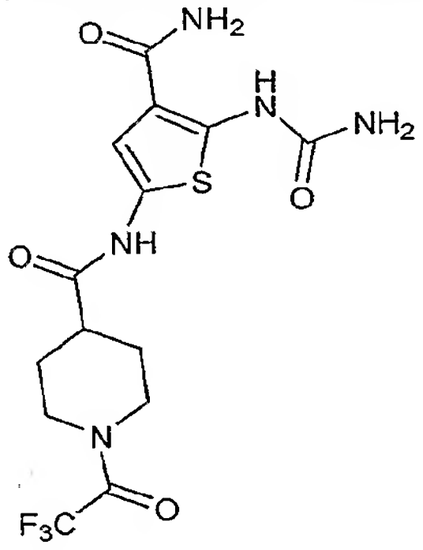
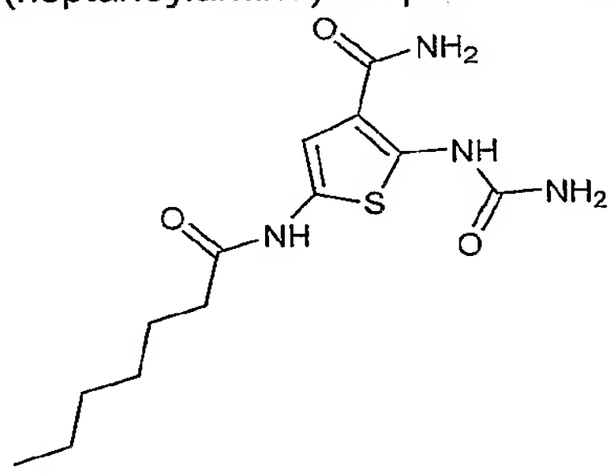
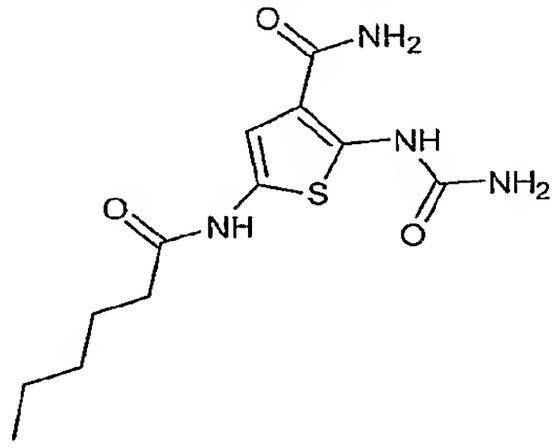
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
180	2-[(aminocarbonyl)amino]-5-({4-[(4-methylpiperazin-1-yl)methyl]benzoyl}amino) thiophene-3-carboxamide 	0.952	417.2	417.1701
181	tert-butyl 2-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}amino) carbonyl]-7-azabicyclo[2.2.1]heptane-7-carboxylate 	2.194	424.2	424.1667
182	2-[(aminocarbonyl)amino]-5-{[(1-cyanocyclopropyl) carbonyl]amino}thiophene-3-carboxamide 	1.193	294.1	294.0679
183	2-[(aminocarbonyl)amino]-5-[(2,2-dimethylpropanoyl)amino] thiophene-3-carboxamide 	1.586	285.1	285.1032
184	2-[(aminocarbonyl)amino]-5-[(3-chloro-2,2-dimethylpropanoyl)amino] thiophene-3-carboxamide 	1.687	319.1	319.0591

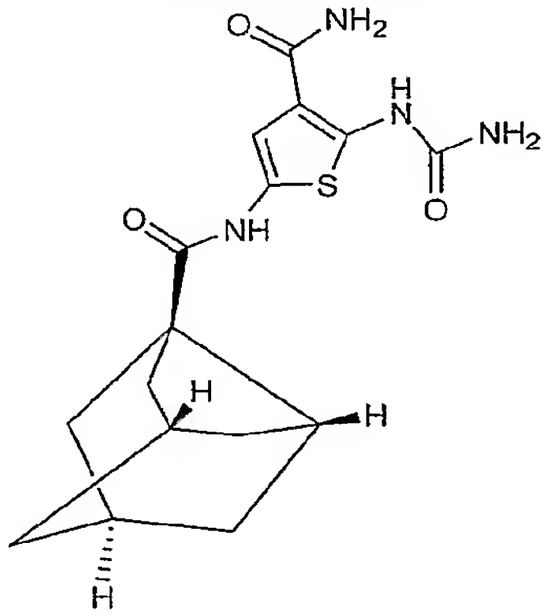
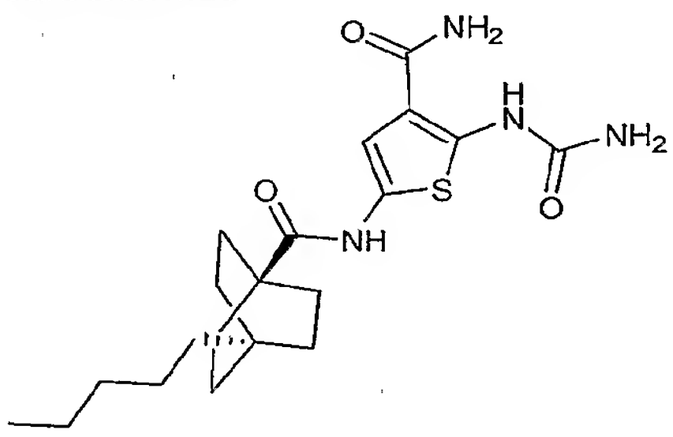
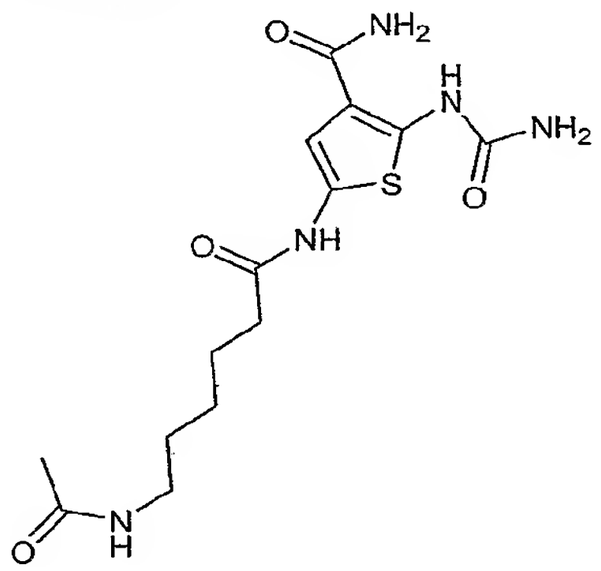
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
185	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}quinoline-4-carboxamide 	1.327	356.1	356.0838
186	2-[(aminocarbonyl)amino]-5-[(2,2-dimethylbutanoyl) amino]thiophene-3-carboxamide 	1.809	299.1	299.1160
187	2-[(aminocarbonyl)amino]-5-({[(1R,2S,3S,4S,6R)-5-oxotricyclo[2.2.1.0~2,6~]hept-3-yl]carbonyl}amino) thiophene-3-carboxamide 	1.342	335.1	335.0784
188	2-[(aminocarbonyl)amino]-5-[(cyclohex-3-en-1-ylcarbonyl)amino] thiophene-3-carboxamide 	1.852	309.1	309.0993

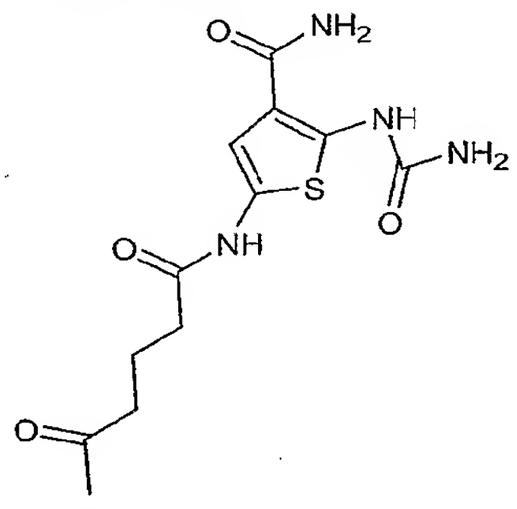
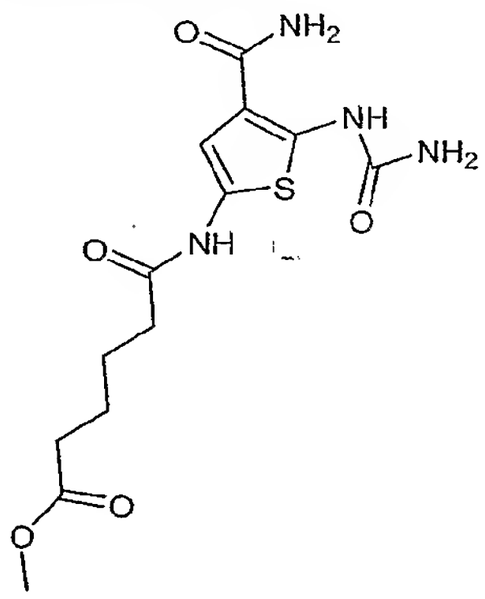
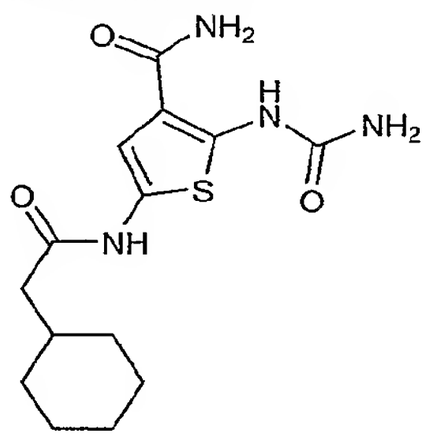
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
189	2-[(aminocarbonyl)amino]-5-[(2,2-dimethylhexanoyl) amino]thiophene-3-carboxamide 	2.358	327.2	327.1487
190	2-[(aminocarbonyl)amino]-5-(propionylamino) thiophene-3-carboxamide 	0.814	257.1	257.0722
191	2-[(aminocarbonyl)amino]-5-({[1-(trifluoromethyl) cyclopropyl]carbonyl} amino)thiophene-3-carboxamide 	1.725	337.1	337.0572
192	2-[(aminocarbonyl)amino]-5-[(4,4,4-trifluoro-2-methylbutanoyl)amino] thiophene-3-carboxamide 	1.715	339.1	339.0735
193	2-[(aminocarbonyl)amino]-5-{[(4-phenylcyclohexyl) carbonyl]amino}thiophene-3-carboxamide 	2.595	387.1	387.1535

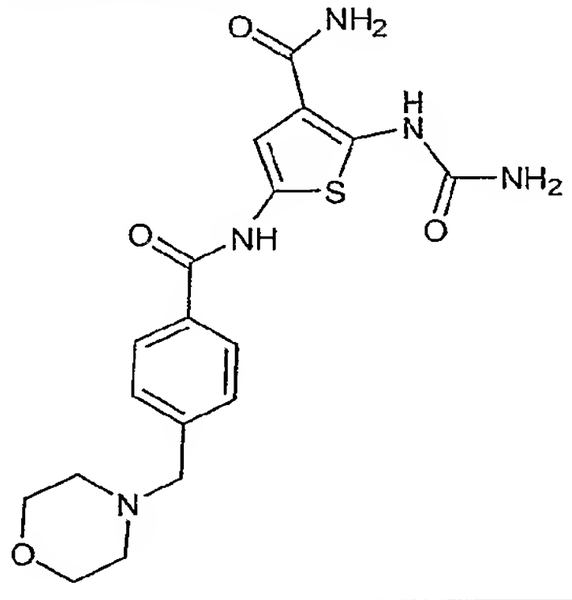
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
194	(1S,2R)-2-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}amino) carbonyl]cyclohexane carboxylic acid 	1.696	355.1	355.1038
195	2-[(aminocarbonyl)amino]-5-[(1,1'-biphenyl-4-ylacetyl)amino]thiophene-3-carboxamide 	2.565	395.1	395.1164
196	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-2-phenylquinoline-3-carboxamide 	2.375	432.1	432.1128
197	2-[(aminocarbonyl)amino]-5-{[(9-oxo-9H-fluoren-4-yl)carbonyl]amino} thiophene-3-carboxamide 	2.184	407.1	407.0787

Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
198	2-[(aminocarbonyl)amino]-5-[(9H-fluoren-1-ylcarbonyl)amino] thiophene-3-carboxamide 	2.590	393.1	393.0995
199	2-[(aminocarbonyl)amino]-5-[(9H-fluoren-4-ylcarbonyl)amino] thiophene-3-carboxamide 	2.377	393.1	393.0987
200	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-3-chloroisonicotinamide 	1.341	340.0	340.0226
201	(1S,2S)-2-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}amino) carbonyl]cyclohexane carboxylic acid 	1.678	355.1	355.1051

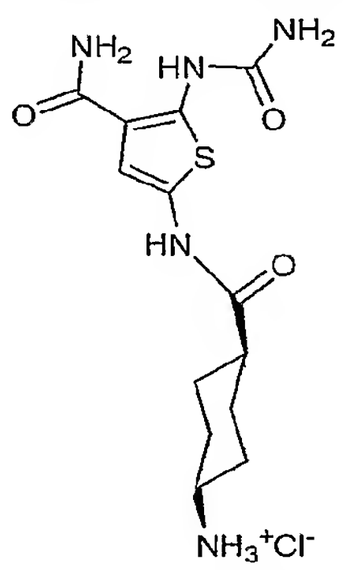
Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
202	2-[(aminocarbonyl)amino]-5-{[6-(benzyloxy)-1-naphthoyl]amino} thiophene-3-carboxamide 	2.862	461.1	461.1230
203	N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}-1-(trifluoroacetyl) piperidine-4-carboxamide 	1.852	408.1	408.095
204	2-[(aminocarbonyl)amino]-5-(heptanoylamino) thiophene-3-carboxamide 	2.255	313.1	313.134
205	2-[(aminocarbonyl)amino]-5-(hexanoylamino) thiophene-3-carboxamide 	1.991	299.1	299.118

Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
206	2-[(aminocarbonyl)amino]-5-{[(2R,5S)-hexahydro-2,5-methanopentalen-3a(1H)-ylcarbonyl]amino} thiophene-3-carboxamide 	2.234	349.1	349.132
207	2-[(aminocarbonyl)amino]-5-{[(4-pentylbicyclo [2.2.2]oct-1-yl)carbonyl] amino}thiophene-3-carboxamide 	3.292	407.2	407.214
208	5-{[6-(acetylamino) hexanoyl]amino}-2-[(aminocarbonyl)amino] thiophene-3-carboxamide 	1.269	356.1	356.139

Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
209	2-[(aminocarbonyl)amino]-5-[(5-oxohexanoyl)amino] thiophene-3-carboxamide 	0.929	313.1	313.099
210	methyl 6-({4-(aminocarbonyl)-5-[(aminocarbonyl)amino] thien-2-yl}amino)-6-oxohexanoate 	1.616	343.1	343.106
211	2-[(aminocarbonyl)amino]-5-[(cyclohexylacetyl) amino]thiophene-3-carboxamide 	2.185	325.1	325.136

Example	Name and Structure	LC (min)	MS (ES^+)	HRMS
212	2-[(aminocarbonyl)amino]-5-{[4-(morpholin-4-ylmethyl)benzoyl]amino} thiophene-3-carboxamide 	1.183	404.1	404.14

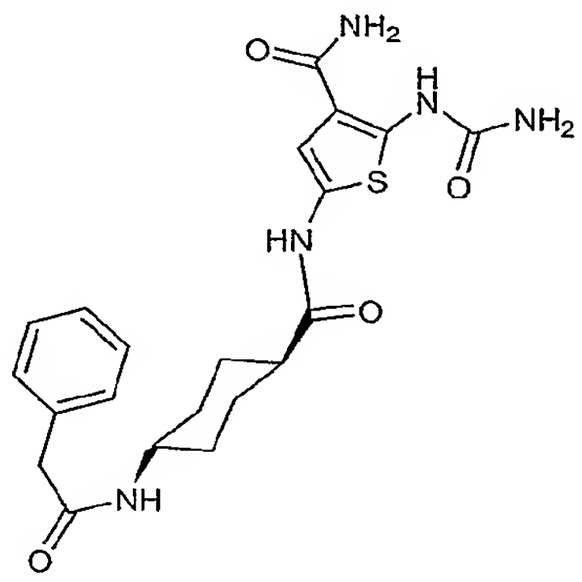
[00507] Example 213: 2-[(Aminocarbonyl)amino]-5-{[(4-aminocyclohexyl)carbonyl]amino}thiophene-3-carboxamide Hydrochloride (trans-isomer)



[00508]

[00509] Three mL of concentrated HCl was added dropwise at room temperature for 3 minutes to 0.1 g of tert-butyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]cyclohexylcarbamate (trans-isomer) (Example 111). The suspension was stirred for 15 minutes, filtered, and washed with 10 mL of chloroform to give the desired product after drying under reduced pressure. ^1H NMR (CD_3OD): δ 1.39-1.59 (m, 2H), 1.60-1.82 (m, 2H), 1.99-2.15 (m, 4H), 2.38-2.52 (m, 1H), 3.09-3.26 (m, 1H), 6.83 (s, 1H). Mass of Molecular Ion: 326 (M + 1).

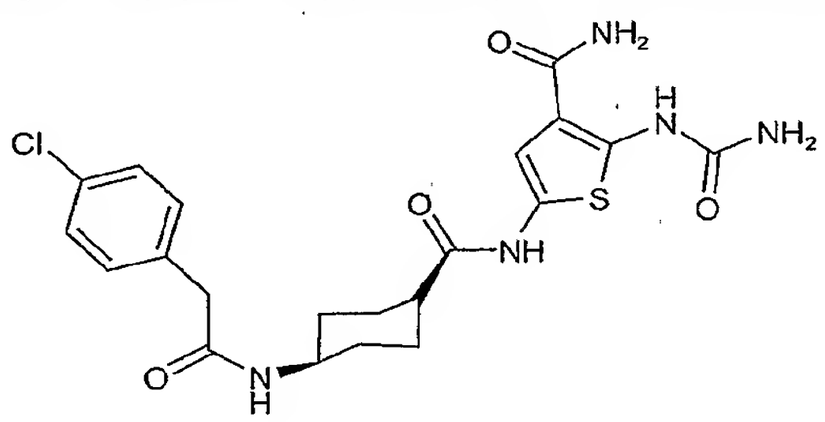
[00510] Example 214: 2-[(aminocarbonyl)amino]-5-[({4-[(phenylacetyl)amino]cyclohexyl}carbonyl)amino]thiophene-3-carboxamide (trans-isomer)



[00511]

[00512] The trans-isomer of 2-[(Aminocarbonyl)amino]-5-{[(4-aminocyclohexyl)carbonyl]amino}thiophene-3-carboxamide (Example 213, 0.07 g, 0.215 mmol) was combined with 0.5 mmol of substituted acetic acid, HBTU (BF_4) 0.17 g (0.5 mmol), N,N-dimethylethylamine (0.3 mL), and DMSO (1.0 mL). The mixture was stirred overnight then most of the liquids were stripped off. The residue was triturated in 80 mL of CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with water (40 mL) overnight, filtered, triturated with 20 mL of a 10% solution of sodium bicarbonate, filtered, washed with water. Then the product was dried under reduced pressure to give the desired amide. ^{1}H NMR (CD_3OD/d_6-DMSO(4:1)): δ 1.08-1.30 (m, 2H), 1.41-1.57 (m, 2H), 1.74-1.92 (m, 4H), 2.14-2.26 (m, 1H), 3.28 (s, 2H), 3.40-3.60 (m, 1H), 6.63 (s, 1H), 7.05-7.30 (m, 5H). Mass of molecular ion: 444 (M + 1).

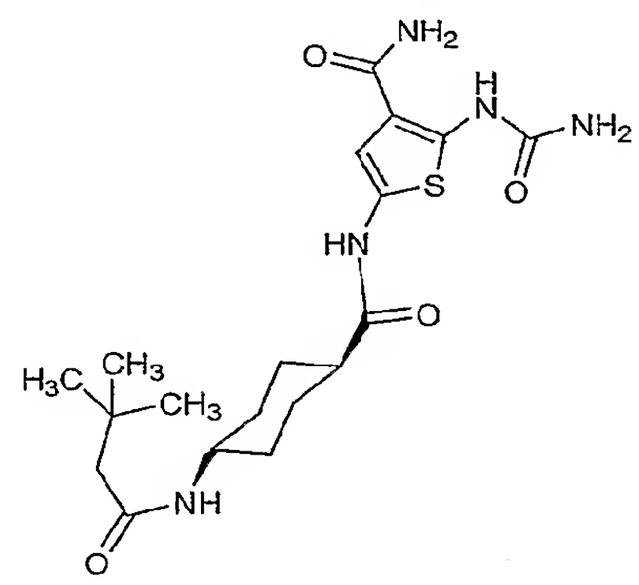
[00513] Example 214.1: 2-[(aminocarbonyl)amino]-5-{[(4-{[(4-chlorophenyl)acetyl]amino}cyclohexyl)carbonyl] amino}thiophene-3-carboxamide



[00514]

[00515] Prepared analogously to Example 214. ^{1}H NMR (CD_3OD/d_6-DMSO(4:1)): δ 1.04-1.26 (m, 2H), 1.39-1.58 (m, 2H), 1.74-1.92 (m, 4H), 2.14-2.28 (m, 1H), 3.38 (s, 2H), 3.40-3.60 (m, 1H), 6.62 (s, 1H), 7.10-7.32 (m, 5H). Mass of Molecular Ion: 478 (M + 1).

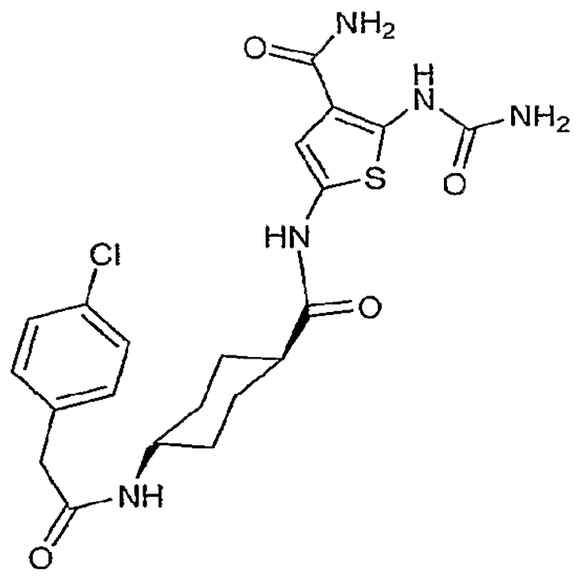
[00516] Example 214.2: 2-[(aminocarbonyl)amino]-5-[({4-[(3,3-dimethylbutanoyl)amino]cyclohexyl}carbonyl)amino] thiophene-3-carboxamide (trans-isomer)



[00517]

[00518] Prepared analogously to Example 214. ^{1}H NMR (CD_3OD/d_6-DMSO(4:1)): δ 0.90 (s, 9H), 1.20-1.40 (m, 2H), 1.50-1.74 (m, 2H), 1.88-2.08 (m, 6H), 2.25-2.38 (m, 1H), 3.58-3.68 (m, 1H), 6.65 (s, 1H). Mass of Molecular Ion: 424 (M + 1).

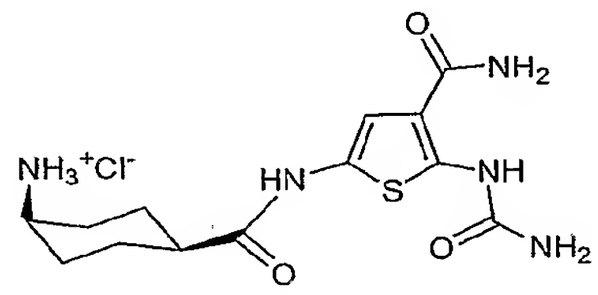
[00519] Example 214.3: 2-[(aminocarbonyl)amino]-5-{[(4-{[(4-chlorophenyl)acetyl]amino}cyclohexyl) carbonyl]amino} thiophene-3-carboxamide (trans-isomer)



[00520]

[00521] Prepared analogously to Example 214. ^{1}H NMR (CD_3OD/d_6-DMSO(4:1)): δ 1.04-1.26 (m, 2H), 1.39-1.58 (m, 2H), 1.74-1.92 (m, 4H), 2.14-2.28 (m, 1H), 3.38 (s, 2H), 3.40-3.60 (m, 1H), 6.62 (s, 1H), 7.10-7.32 (m, 5H). Mass of Molecular Ion: 478 (M + 1).

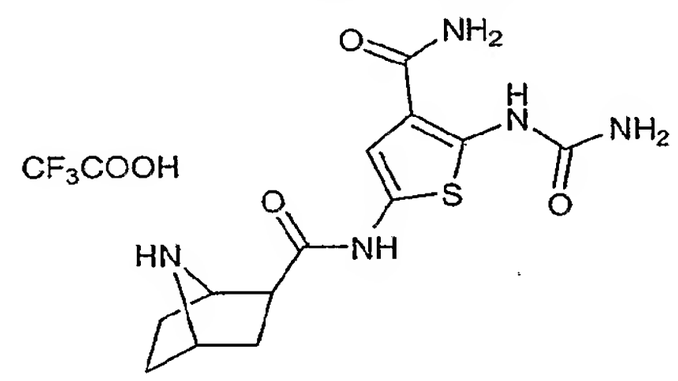
[00522] Example 215: 2-[(Aminocarbonyl)amino]-5-{[(4-aminocyclohexyl)carbonyl]amino}thiophene-3-carboxamide Hydrochloride (cis-isomer)



[00523]

[00524] Prepared according to Example 213. ^{1}H NMR (CD_3OD): δ 1.70-1.84 (m, 2H), 1.85-1.94 (m, 4H), 1.98-2.10 (m, 2H), 2.61-2.72 (m, 1H), 3.24-3.36 (m, 1H), 6.79 (s, 1H). Mass of Molecular Ion: 326 (M + 1).

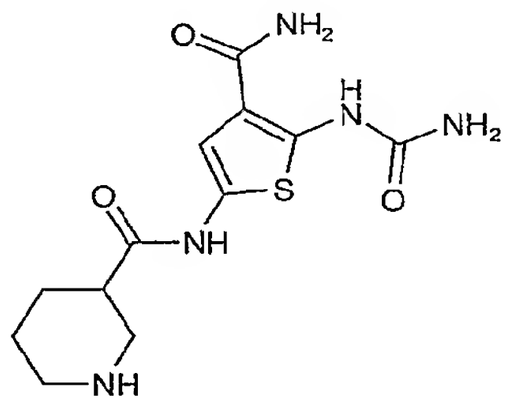
[00525] Example 216: N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}-7-azabicyclo[2.2.1] heptane-2-carboxamide trifluoroacetate



[00526]

[00527] To tert-butyl 2-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}amino)carbonyl]-7-azabicyclo[2.2.1]heptane-7-carboxylate (Example 181, 760.069 g, 0.163 mmol) in a 2 dram vial was added 2.0 mL trifluoroacetic acid and 2.0 mL dichloromethane. The reaction mixture was stirred for one hour at room temperature and the reaction progress was monitored by HPLC. Volatiles were removed via nitrogen stream and the crude reaction mixture was dried under high vacuum overnight to afford a mauve solid. ^{1}H NMR (d^6-DMSO, 400 MHz) δ 1.63 (m, 2H), 1.81 (m, 2H), 1.93-2.05 (m, 2H), 2.92 (dd, 1H, J = 8.8 Hz, J = 5.2 Hz), 4.14 (s, 1H), 4.32 (s, 1H), 6.76 (s, 3H), 7.16 (brs, 1H), 7.59 (brs, 1H), 8.06 (d, 1H, J = 8.4 Hz), 9.03 (d, 1H, J = 8.8 Hz), 10.82 (s, 1H), 11.07 (s, 1H); ^{19}F NMR (d^6-DMSO) δ -74.4 (CF_3, s); LC (min) 0.380 (100%); MS (ES+) 324 (M+1); HRMS (ES+) *m/z* calc'd for ($C_{13}H_{17}N_5O_3S$) 324.1125, found 324.1110.

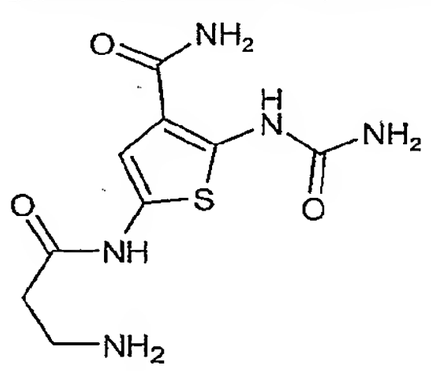
[00528] Example 217: N-{4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}piperidine-3-carboxamide



[00529]

[00530] Prepared analogously to Example 216. LC (min) 0.355 (100%); MS (ES+) 312 (M+1); HRMS (ES+) *m/z* found 312.1144.

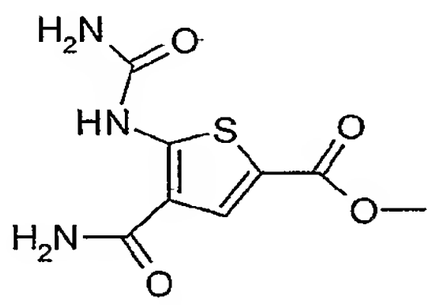
[00531] Example 218: 5-(beta-alanylamino)-2-[(aminocarbonyl)amino]thiophene-3-carboxamide



[00532]

[00533] Prepared analogously to Example 216. LC (min) 0.196 (100%); MS (ES+) 272 (M+1); HRMS (ES+) *m/z* found 272.0811.

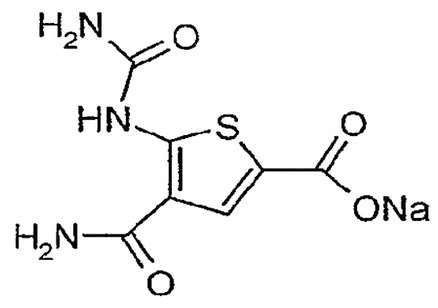
[00534] Example 300: Methyl 4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thiophene-2-carboxylate



[00535]

[00536] 2-[(aminocarbonyl)amino]-5-bromothiophene-3-carboxamide (1.70 g, 6.4 mmol), DPPF (1,1'-bis(diphenylphosphino)ferrocene) (0.382 g, 0.6 mmol), DMF (N,N-dimethylformamide) (24 mL), and methanol (20 mL) were combined in a tube containing a stir-bar. Nitrogen was bubbled through the solution for 30 minutes to remove oxygen, after that $Pd(OAc)_2$ (0.166 g, 0.74 mmol) was added, and the tube with reaction mixture was purged with nitrogen. The tube was placed in an oil bath at 80°C, and CO was bubbled for 6 hours under vigorous stirring. The reaction mixture was filtered through celite, washed with 10 mL of DMF. Most of the liquids were removed under reduced pressure, and 60 mL of methylene chloride was added to the residue. The mixture was triturated for 2 hours, filtered, and dried. The solid was triturated with water (60 mL) for 5 hours, filtered, dried, and triturated with 25 mL of ethanol overnight, to give the desired product after filtration and drying. ^{1}H NMR (d_6-DMSO): δ 3.78 (s, 3H), 6.82-7.35 (br s, 2H), 7.39 (br s, 1H), 7.72 (br s, 1H), 8.16 (s, 1H), 11.30 (s, 1H). ESI mass spectrum for $C_8H_9N_3O_4S^+$: 244 (M + 1).).

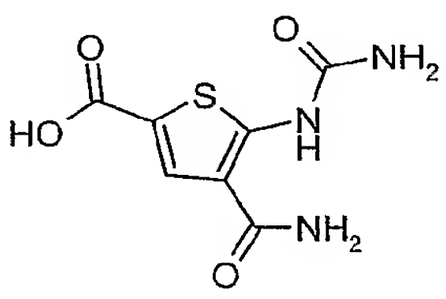
[00537] Example 301: Sodium 4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thiophene-2-carboxylate



[00538]

[00539] Methyl 4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thiophene-2-carboxylate (Example 300, 0.60 g, 2.5 mmol), 4.8 mL of 1N NaOH, and 1 mL of CH_3OH were placed in a flask containing a stir-bar. The mixture was stirred overnight at room temperature. Liquids were removed under reduced pressure, solid was dried and triturated with 30 mL of ethanol for 6 hours to give the desired salt after filtration and drying. ^1H NMR (D_2O): δ 7.43 (s, 1H). ESI mass spectrum for $C_7H_6N_3O_4S^+$: 230 (M + 1).

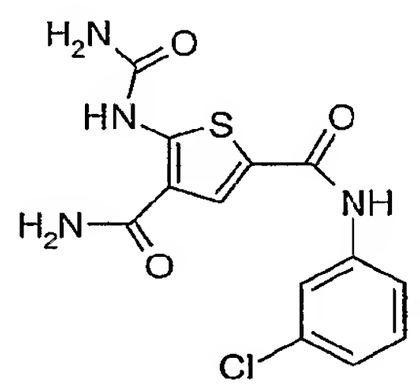
[00540] Example 302: 4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thiophene-2-carboxylic acid



[00541]

[00542] 4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thiophene-2-carboxylic acid, sodium salt (Example 301, 0.45 g, 1.8 mmol) was dissolved in a minimal amount of H_2O, and 6N HCl was added to adjust the pH to 3. The precipitate was filtered, washed with sodium bicarbonate solution and water. After drying, the desired acid was obtained. ^1H NMR (d_6-DMSO): δ 6.88-7.23 (br s, 2H), 7.35 (br s, 1H), 7.73 (br s, 1H), 8.06 (s, 1H), 11.24 (s, 1H), 12.02-13.22 (br s, 1H). ESI mass spectrum for $C_7H_6N_3O_4S^+$: 230 (M + 1).

[00543] Example 303: 5-[(Aminocarbonyl)amino]-N-2-(3-chlorophenyl)thiophene-2,4-dicarboxamide

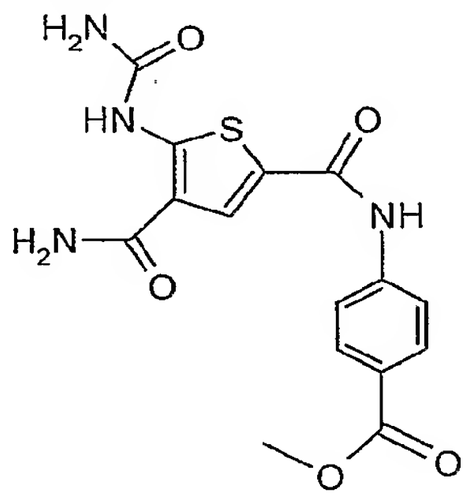


[00544]

[00545] 4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thiophene-2-carboxylic acid (Example 302, 0.1 g, 0.43 mmol) was combined with 1.5 mmol of an aniline derivative, HBTU (BF_4) (1.5 mmol), N,N-dimethylethylamine (0.5 mL, 4.5 mmol), and DMSO (1.0 mL). The mixture was stirred for 20 hours at 50°C, then most of the liquids were stripped off. The residue was triturated in 60 mL of CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with saturated sodium bicarbonate solution (60 mL) overnight, washed with water, filtered, and triturated with 5 mL of ethanol. After filtration the product was dried under reduced pressure. The title compound is a solid. ^1H NMR (CD_3OD)/d_6-DMSO (4:1): δ 7.07 (dd, 1H, J = 8.8, 1.20

Hz), 7.28 (t, 1H, J = 8.1 Hz), 7.57 (dd, 1H, J = 7.1, 1.0 Hz), 7.83 (t, 1H, J = 2.0 Hz), 7.98 (s, 1H). ESI mass spectrum for $C_{13}H_{11}ClN_4O_3S^+$: 339 (M + 1).

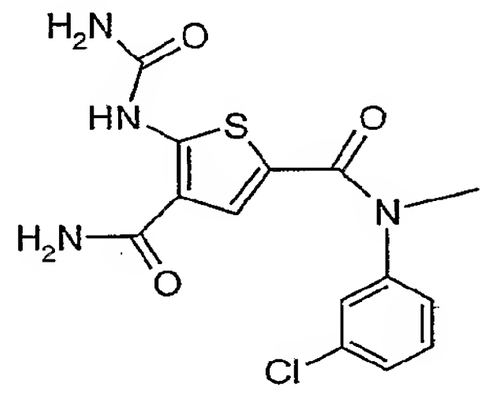
[00546] Example 304: Methyl 4-[({4-(aminocarbonyl)-5-[(aminocarbonyl)amino]thien-2-yl}carbonyl)amino]benzoate



[00547]

[00548] Prepared analogously to Example 303. The title compound is a solid. ^{1}H NMR (CD_3OD)/d_6-DMSO (4:1): δ 3.79 (s, 3H), 7.79 (d, 2H, J = 8.9 Hz), 7.97-8.38 (m, 3H). ESI mass spectrum for $C_{15}H_{14}N_4O_5S^+$: 363 (M + 1).

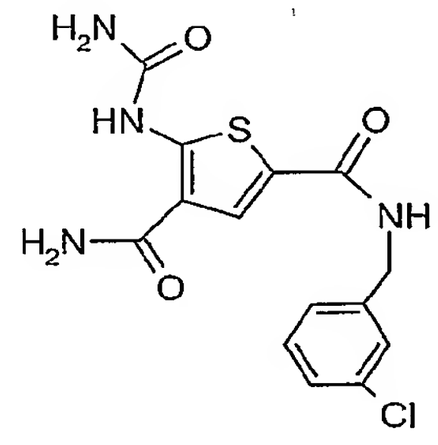
[00549] Example 305: 5-[(Aminocarbonyl)amino]-N-2-(3-chlorophenyl)-N-2-methylthiophene-2,4-dicarboxamide



[00550]

[00551] Prepared analogously to Example 303. The title compound is a solid. ^{1}H NMR (CD_3OD)/d_6-DMSO (4:1): δ 3.33 (s, 3H), 7.11-7.20 (m, 1H), 7.25-8.38 (m, 4H). ESI mass spectrum for $C_{14}H_{13}ClN_4O_3S^+$: 353 (M + 1).

[00552] Example 306: 5-[(Aminocarbonyl)amino]-N-2-(3-chlorobenzyl)thiophene-2,4-dicarboxamide

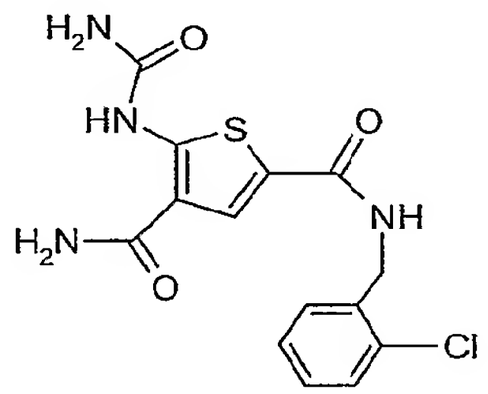


[00553]

[00554] 4-(Aminocarbonyl)-5-[(aminocarbonyl)amino]thiophene-2-carboxylic acid (Example 302, 0.1 g, 0.43 mmol) was combined with 1.5 mmol of an alkyl- or alkylaryl- amine, HBTU (BF_4) (1.5 mmol), N,N-diisopropylethylamine (0.5 mL, 4.5 mmol), and DMSO (1.0 mL). The mixture was stirred for 20 hours

at room temperature, then most of liquids were stripped off. The residue was triturated in 60 mL of CH_2Cl_2 for 6 hours. The slurry was filtered, triturated with saturated sodium bicarbonate solution (60 mL) overnight, washed with water, filtered, and triturated with 5 mL of ethanol. After filtration the product was dried under reduced pressure. The title compound is a solid. ^{1}H NMR (CD_3OD)/d_6-DMSO (4:1): δ 3.89 (s, 2H), 7.18-7.24 (m, 4H), 7.69 (s, 1H). ESI mass spectrum for $C_{14}H_{13}ClN_4O_3S^+$: 353 (M + 1).

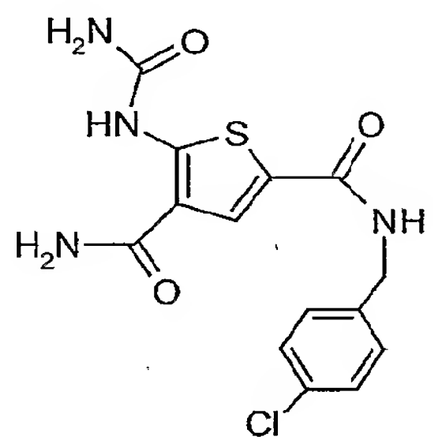
[00555] Example 307: 5-[(Aminocarbonyl)amino]-N-2-(2-chlorobenzyl)thiophene-2,4-dicarboxamide



[00556]

[00557] Prepared analogously to Example 306. The title compound is a solid. ^{1}H NMR d_6-DMSO: δ 4.46 (d, 2H, J = 5.6 Hz), 7.07 (br s, 2H), 7.20-7.48 (m, 5H), 7.93 (s, 1H), 8.60 (t, 1H, J = 5.7 Hz), 11.05 (s, 1H). ESI mass spectrum for $C_{14}H_{13}ClN_4O_3S^+$: 353 (M + 1).

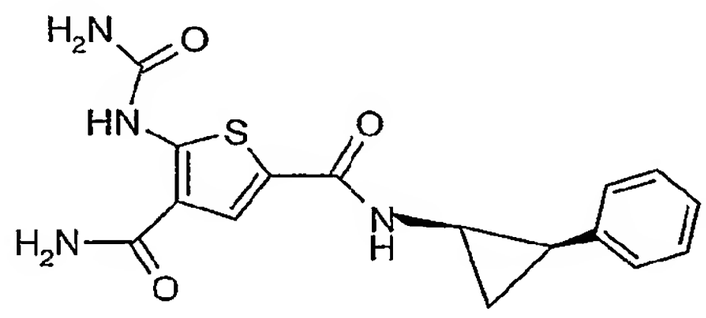
[00558] Example 308: 5-[(Aminocarbonyl)amino]-N-2-(4-chlorobenzyl)thiophene-2,4-dicarboxamide



[00559]

[00560] Prepared analogously to Example 306. The title compound is a solid. ^{1}H NMR d_6-DMSO: δ 4.36 (d, 2H, J = 5.6 Hz), 7.06 (br s, 2H), 7.29 (d, 2H, J = 8.2 Hz), 7.38 (d, 2H, J = 8.3 Hz), 7.89 (s, 1H), 8.64 (t, 1H, J = 5.6 Hz), 11.04 (s, 1H). ESI mass spectrum for $C_{14}H_{13}ClN_4O_3S^+$: 353 (M + 1).

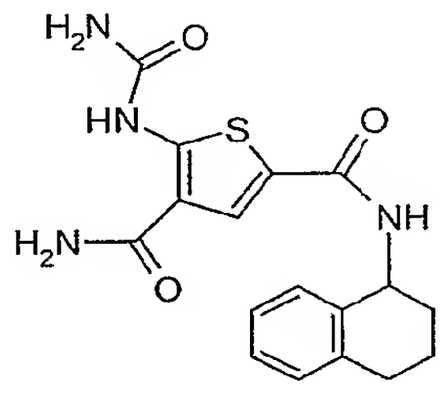
[00561] Example 309: 5-[(Aminocarbonyl)amino]-N-2-[(1R,2R)-2-phenylcyclopropyl]thiophene-2,4-dicarboxamide



[00562]

[00563] Prepared analogously to Example 306. The title compound is a solid. ^{1}H NMR (CD_3OD)/d_6-DMSO (4:1): δ 1.20-1.35 (m, 2H), 2.00-2.18 (m, 1H), 2.81-2.98 (m, 1H), 7.01-7.30 (m, 5H), 7.68 (s, 1H). ESI mass spectrum for $C_{16}H_{16}N_4O_3S^+$: 345 (M + 1).

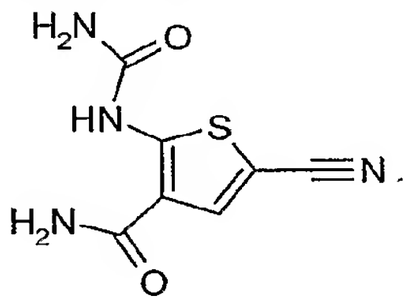
[00564] Example 310: 5-[(Aminocarbonyl)amino]-N-2-1,2,3,4-tetrahydronaphthalen-1-ylthiophene-2,4-dicarboxamide



[00565]

[00566] Prepared analogously to Example 306. The title compound is a solid. ^{1}H NMR (CD_3OD): δ 1.80-2.18 (m, 4H), 2.72-2.98 (m, 2H), 5.25 (t, 1H, J = 6.8 Hz), 7.08-7.30 (m, 4H), 7.69 (s, 1H). ESI mass spectrum for $C_{17}H_{18}N_4O_3S^+$: 359 (M + 1).

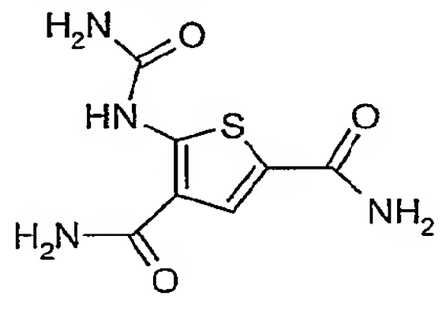
[00567] Example 311: 2-[(aminocarbonyl)amino]-5-cyanothiophene-3-carboxamide



[00568]

[00569] 2-[(aminocarbonyl)amino]-5-bromothiophene-3-carboxamide (4.48 g, 18 mmol), $Zn(CN)_2$ (1.247 g, 10.9 mmol), DPPF (1,1'-bis(diphenylphosphino)ferrocene) (1.308 g, 2.35 mmol), DMF (N,N-dimethylformamide) (39 mL), and benzonitrile (13 mL) were combined in a flask containing a stir-bar. Nitrogen was bubbled through the solution for 30 minutes to remove oxygen, after that $Pd_2(dba)_3$ (0.97 g, 1.04 mmol) was added, and the flask with reaction mixture was purged with nitrogen. The flask was placed in an oil bath at 90°C for 6 hours with vigorous stirring. The reaction mixture was filtered through celite, washed with 10 mL of DMF. Most of the liquids were removed under reduced pressure, and 100 mL of methylene chloride was added to the residue. The mixture was triturated for 1 hour, filtered, and dried. The solid was triturated with water (100 mL) for 3 hours, filtered and dried. The solid was placed in a flask containing half the amount of the above used reagents and solvents, and the reaction was repeated under the same conditions, including work up, to give the desired product after trituration with methanol (50 mL), filtration and drying. ^{1}H NMR (CD_3OD): 7.90 (s, 1H). ESI mass spectrum for $C_7H_6N_4O_2S^+$: 211 (M + 1).).

[00570] Example 312: 5-[(aminocarbonyl)amino] thiophene-2,4-dicarboxamide



[00571]

[00572] 2-[(aminocarbonyl)amino]-5-cyanothiophene-3-carboxamide (Example 311, 0.21 g, 1.0 mmol), 2 mL of 1N NaOH, and 1 mL of CH_3OH were placed in a flask containing a stir-bar. The mixture was stirred overnight at room temperature. Liquids were removed under reduced pressure, solid

was dried and triturated with 10 mL of ethanol for 6 hours to give the desired amide, after filtration and drying. ^{1}H NMR d_6-DMSO: δ 5.20 (s, 2H), 6.39 (s, 1H), 6.41-7.00 (br s, 3H), 7.67 (s, 1H), 9.90 (s, 1H). ESI mass spectrum for $C_7H_8N_4O_3S^+$: 229 (M + 1).

[00573] Example 400: IKK-2 IC_{50} determination

Materials

[00574] SAM$^{2\ TM}$ 96 Biotin capture plates were from Promega. Anti-FLAG affinity resin, FLAG-peptide, NP-40 (Nonidet P-40), BSA, ATP, ADP, AMP, LPS (*E. coli* serotype 0111:B4), and dithiothreitol were obtained from Sigma Chemicals. Antibodies specific for NEMO (IKK-γ) (FL-419), IKK-1(H-744), IKK-2(H-470) and IκBα(C-21) were purchased from Santa Cruz Biotechnology. Ni-NTA resin was purchased from Qiagen. Peptides were purchased from American Peptide Company. Protease inhibitor cocktail tablets were from Boehringer Mannheim. Sephacryl S-300 column was from Pharmacia LKB Biotechnology. Centriprep-10 concentrators with a molecular weight cutoff of 10 kDa and membranes with molecular weight cut-off of 30 kDa were obtained from Amicon. [Υ-^{33}P] ATP (2500 Ci/mmol) and [Υ-^{32}P] ATP (6000 Ci/mmol) were purchased from Amersham. The other reagents used were of the highest grade commercially available.

Cloning and Expression

[00575] cDNAs of human IKK-1 and IKK-2 were amplified by reverse transcriptase-polymerase chain reaction from human placental RNA (Clonetech). hIKK-1 was subcloned into pFastBac HTa (Life Technologies) and expressed as N-terminal His_6-tagged fusion protein. The hIKK-2 cDNA was amplified using a reverse oligonucleotide primer which incorporated the peptide sequence for a FLAG-epitope tag at the C-terminus of the IKK-2 coding region (DYKDDDDKD). The hIKK-2:FLAG cDNA was subcloned into the baculovirus vector pFastBac. The rhIKK-2 (S177S, E177E) mutant was constructed in the same vector used for wild type rhIKK-2 using a QuikChange^{TM} mutagenesis kit (Stratagene). Viral stocks of each construct were used to infect insect cells grown in 40L suspension culture. The cells were lysed at a time that maximal expression and rhIKK activity were demonstrated. Cell lysates were stored at -80°C until purification of the recombinant proteins was undertaken as described below.

Enzyme Isolation

[00576] All purification procedures were carried out at 4°C unless otherwise noted. Buffers used are: buffer A: 20 mM Tris-HCl, pH 7.6, containing 50 mM NaCl, 20 mM NaF, 20 mM β-Glycerophosphate, 500 uM sodium orthovanadate, 2.5 mM metabisulfite, 5 mM benzamidine, 1 mM EDTA, 0.5 mM EGTA, 10% glycerol, 1 mM DTT, 1X Complete^{TM} protease inhibitors; buffer B: same as buffer A, except 150 mM NaCl, and buffer C: same as buffer A, except 500 mM NaCl.

Isolation of rhIKK-1 homodimer

[00577] Cells from an 8-liter fermentation of baculovirus-expressed IKK-1 tagged with His peptide were centrifuged and the cell pellet (MOI 0.1, I=72 hr) was re-suspended in 100 ml of buffer C. The cells were microfluidized and centrifuged at 100,000 X g for 45 min. The supernatant was collected, imidazole added to the final concentration of 10 mM and incubated with 25 ml of Ni-NTA resin for 2 hrs. The suspension was poured into a 25 ml column and washed with 250 ml of buffer C and then with 125 ml of 50 mM imidazole in buffer C. rhIKK-1 homodimer was eluted using 300 mM imidazole in buffer C. BSA

and NP-40 were added to the enzyme fractions to the final concentration of 0.1 %. The enzyme was dialyzed against buffer B, aliquoted and stored at -80°C.

Isolation of rhIKK-2 homodimer

[00578] A 10-liter culture of baculovirus-expressing IKK-2 tagged with FLAG peptide was centrifuged and the cell pellet (MOI=0.1 and I=72 hrs) was re-suspended in buffer A. These cells were microfluidized, and centrifuged at 100,000 X g for 45 min. Supernatant was passed over a G-25 column equilibrated with Buffer A. Protein peak was collected and incubated with anti-FLAG affinity resin on a rotator overnight in buffer B. The resin was washed in batch with 10-15 bed volumes of buffer C. Washed resin was poured into a column and rhIKK-2 homodimer was eluted using 5 bed volumes of buffer B containing FLAG peptide. 5 mM DTT, 0.1% NP-40 and BSA (concentrated to 0.1% in final amount) was added to the eluted enzyme before concentrating in using an Amicon membrane with a molecular weight cut-off of 30 kDa. Enzyme was aliquoted and stored at -80°C.

Isolation of rhIKK-1/IKK-2 heterodimer

[00579] The heterodimer enzyme was produced by coinfection in a baculovirus system (FLAG IKK-2/IKK-1 His; MOI=0.1 and I=72 hrs). Infected cells were centrifuged and the cell pellet (10.0 g) was suspended in 50 ml of buffer A. The protein suspension was microfluidized and centrifuged at 100,000 X g for 45 min. Imidazole was added to the supernatant to a final concentration of 10 mM. The protein was allowed to bind 25 ml of Ni-NTA resin by mixing for 2 hrs. The protein-resin slurry was poured into a 25 ml column and washed with 250 ml of buffer A containing 10 mM imidazole followed by 125 ml of buffer A containing 50 mM imidazole. Buffer A, containing 300 mM imidazole, was then used to elute the protein. A 75 ml pool was collected and NP-40 was added to a final concentration of 0.1%. The protein solution was then dialyzed against buffer B. The dialyzed heterodimer enzyme was then allowed to bind to 25 ml of anti-FLAG M2 agarose affinity gel overnight with constant mixing. The protein-resin slurry was then centrifuged for 5 min at 2,000 rpm. The supernatant was collected and the resin re-suspended in 100 ml of buffer C containing 0.1% NP-40. The resin was washed with 375 ml of buffer C containing 0.1 % NP-40. The protein-resin was poured into a 25 ml column and the enzyme eluted using buffer B containing FLAG peptide. Enzyme fractions (100 ml) were collected and concentrated to 20 ml using an Amicon membrane with molecular weight cut-off of 30 kDa. Bovine serum albumin was added to the concentrated enzyme to final concentration of 0.1 %. The enzyme was then aliquoted and stored at -80°C.

Cell Culture

[00580] The wild type (wt) human pre-B cell line, 70Z/3, and its mutant, 1.3E2, were generously provided by Dr. Carol Sibley. Wt 70Z/3 and 1.3E2 cells were grown in RPMI 1640 (Gibco) supplemented with 7 % defined bovine serum (Hyclone) and 50 μM 2-mercaptoethanol. Human monocytic leukemia THP-1 cells, obtained from ATCC, were cultured in RPMI 1640 supplemented with 10% defined bovine serum, 10 mM HEPES, 1.0 mM sodium pyruvate and 50 μM 2-mercaptoethanol. For experiments, cells were plated in 6 well plates at $1x10^6$ cells/ml in fresh media. Pre-B cells were stimulated by the addition of 10 μg/ml LPS for varying lengths of time ranging from 0-4 hr. THP-1 cells were stimulated by the addition of 1 μg/ml LPS for 45 minutes. Cells were pelleted, washed with cold 50 mM sodium phosphate buffer, pH 7.4 containing 0.15 M NaCl and lysed at 4°C in 20 mM Hepes buffer, pH 7.6 containing 50 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM sodium orthovanadate, 10 mM β-glycerophosphate, 1 mM NaF, 1 mM

PMSF, 1 mM DTT and 0.5 % NP40 (lysis buffer). The cytosolic fractions obtained following centrifugation at 10,000 X g were stored at -80°C until used.

Immunoprecipitation and Western Blotting

[00581] SF9 cells paste containing rhIKKs were centrifuged (100,000 X g, 10 min) to remove debris. rhIKKs were immunoprecipitated (100 μg of cell paste) from the cell supernatant using 3 μg of anti-NEMO antibody (FL-419), followed by coupling to protein A sepharose beads. rhIKKs were also immunoprecipitated from affinity chromatography purified protein preparations (1 μg) using anti-FLAG, anti-His or anti-NEMO antibodies (1-4 μg) followed by protein A sepharose coupling. The native, human IKK complex was immunoprecipitated from THP-1 cell homogenates (300 μg/condition) using the anti-NEMO antibody. Immune complexes were pelleted and washed 3 times with 1 ml cold lysis buffer. Immunoprecipitated rhIKKs were chromatographed by SDS-PAGE (8% Tris-glycine) and transferred to nitrocellulose membranes (Novex) and detected by chemiluminescense (SuperSignal) using specific anti-IKK antibodies (IKK-2 H-470, IKK-1 H-744). Native IKK-2, IκBα, and NEMO proteins from cytosolic lysates (20-80 μg) were separated by SDS-PAGE and visualized by chemiluminescense using specific antibodies.

Phosphatase Treatment

[00582] Immunoprecipitated rhIKKs were washed 2 times in 50 mM Tris-HCl, pH 8.2 containing 0.1 mM EDTA, 1 mM DTT, 1 mM PMSF and 2 mM $MnCl_2$ and resuspended in 50 μl. Phosphatase (λPPase, 1000 U) was pre-diluted in the same buffer and added to the IKK samples. Following incubation at room temperature for 30 minutes with intermittent mixing, cold lysis buffer was added to the tubes to stop the reaction. After several washes, 10 % of the beads were removed for Western analysis, and the remaining material was pelleted and resuspended in 100 μl of the buffer used for the *in vitro* kinase assay.

IKK-1 SAM Enzyme Assay

[00583] IKK-1 kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu), a SAM$^{2\ TM}$ 96 Biotin capture plate and a vacuum system. The standard reaction mixture contained 5 μM biotinylated IκBα peptide, 1 μM [γ-^{33}P] ATP (about 1 X 10^5 cpm), 1 mM DTT, 50 mM KCl, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 10 mM NaF, 25 mM Hepes buffer, pH. 7.6 and enzyme solution (1-10 μl) in a final volume of 50 μl. After incubation at 25°C for 30 min, 25 μl of the reaction mixture was withdrawn and added to a SAM$^{2\ TM}$ 96 Biotin capture 96-well plate. Each well was then washed successively with 800 μl 2 M NaCl, 1.2 ml of NaCl containing 1% H_3PO_4, 400 μl H_2O, and 200 μl 95% ethanol. The plate was allowed to dry in a hood at 25°C for 1 hr and then 25 μl of scintillation fluid (Microscint 20) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard). Under each assay condition, the degree of phosphorylation of IκBα peptide substrate was linear with time and concentration for all purified enzymes. Results from the biotinylated peptide assay were confirmed by SDS-PAGE analysis of kinase reaction utilizing a GST-IκB$\alpha_{1\text{-}54}$ and [γ-^{32}P] ATP. The resulting radiolabeled substrate was quantitated by Phosphoimager (Molecular Dynamics). An ion exchange resin assay was also employed using [γ-^{33}P] ATP and GST-IκB$\alpha_{1\text{-}54}$ fusion protein as the substrates. Each assay system yielded consistent results in regard to K_m and specific activities for each of the purified kinase isoforms. One unit of enzyme activity was defined as the amount required to catalyze the transfer of 1 nmole of phosphate from ATP to IκBα peptide per min. Specific activity was expressed as units per mg of protein. For experiments related to K_m

determination of purified enzymes, various concentrations of ATP or IκBα peptide were used in the assay at either a fixed IκBα or ATP concentration. For IκBα peptide K_m, assays were carried out with 0.1 μg of enzyme, 5 μM ATP and IκBα peptide from 0.5 to 20μM. For ATP K_m, assays were carried out with 0.1 μg of enzyme, 10 μM IκBα peptide and ATP from 0.1 to 10μM. For K_m determination of rhIKK-1 homodimer, due to its low activity and higher K_m for IκBα peptide, rhIKK-1 homodimer (0.3 μg) was assayed with 125 μM IκBα peptide and a 5-fold higher specific activity of ATP (from 0.1 to 10 μM) for ATP K_m experiments and a 5-fold higher specific activity of 5 μM ATP and IκBα peptide (from 5 to 200 μM) for IκBα peptide K_m experiments.

IKK heterodimer Resin Enzyme Assay

[00584] IKK heterodimer kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 ul of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μl enzyme solution and 10 μl inhibitor in a final volume of 50 μl. After incubation at 25°C for 30 min, 150 μl resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50 ul of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μl of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

IKK-2 Resin Enzyme Assay

[00585] IKK-2 kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 ul of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μl enzyme solution and 10 ul inhibitor in a final volume of 50 μl. After incubation at 25°C for 30 min, 150 μl resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50 ul of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μl of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

[00586] IKK-2 IC_{50} values obtained from the assay described above are shown in Table XI.

Table XI

Example No.	IKK-2 IC_{50} (μM)
3	0.0537
4	0.0645
5	0.0932
6	0.0952
7	0.298
8	0.351

Example No.	IKK-2 IC_{50} (μM)
9	0.038
10	0.045
11	0.318
12	0.341
13	0.346
14	0.385

Example No.	IKK-2 IC_{50} (μM)
15	0.393
16	1.01
17	7.10
18	0.0995
19	0.192
20	0.316

Example No.	IKK-2 IC_{50} (μM)
21	0.210
22	0.178
23	0.138
24	0.0991
25	0.0794
26	0.0684
27	0.0554
28	0.203
29	0.647
30	0.659
31A	8.84
31B	8.84
32	>20
33	0.272
34	0.501
35	0.0307
36	0.617
37	0.0617
38	0.0355
39	0.104
40	0.162
41	0.180
42	0.0718
43	0.040
44	0.597
45	0.221
46	0.0448
47	0.152
48	0.140
49	0.240
50	0.266
51	>20
52	1.65
53	1.98
54	0.0155
55	0.0537
56	0.0676
57	0.0474
58	0.0441
59	0.0410

Example No.	IKK-2 IC_{50} (μM)
60	0.0308
61	0.113
62	0.0254
63	0.0498
64	0.0223
65	0.0941
66	0.0335
67	0.0156
68	0.401
69	0.131
70	0.0217
71	0.0495
72	0.0704
73	0.180
74	0.0870
75	0.0463
76	0.0421
77	0.0444
78	0.179
79	3.14
80	2.23
81	2.62
82	20
83	11.5
84	5
85	5.79
86	3.98
87	4.02
88	9.79
89	6.3
90	6.22
91	3.86
92	13.7
93	20
94	18.3
95	10.6
96	2.81
97	3.53
98	20
99	6.37

Example No.	IKK-2 IC_{50} (μM)
100	5.78
101	1.05
102	0.053
103	0.413
104	0.0453
105	0.166
109	0.0773
110	0.0480
110.1	0.166
111	0.0967
112	0.119
113	0.162
114	0.548
115	0.045
116	0.296
117	0.0101
118	0.0362
119	0.0423
120	0.0459
121	0.0570
122	0.0576
123	0.0598
124	0.0633
125	0.0673
126	0.0689
127	0.0692
128	0.0162
129	0.0836
130	0.0850
131	0.0873
132	0.0892
133	0.0918
134	0.0999
135	0.106
136	0.107
137	0.115
138	0.123
139	0.0177
140	0.135
141	0.135

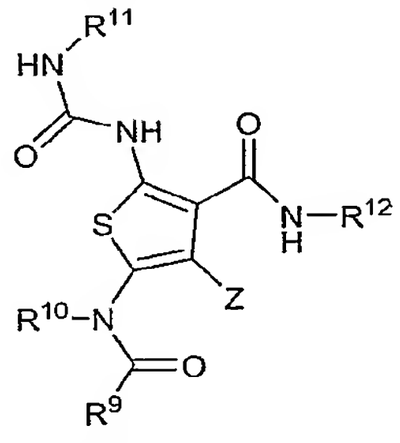
Example No.	IKK-2 IC_{50} (μM)
142	0.136
143	0.137
144	0.145
145	0.147
146	0.163
147	0.164
148	0.169
149	0.181
150	0.0215
151	0.183
152	0.193
153	0.200
154	0.240
155	0.247
156	0.261
157	0.271
158	0.353
159	0.361
160	0.411
161	0.0218
162	0.498
163	0.633
164	0.657
165	1.15
166	1.26
167	1.27
168	1.31
169	1.87
170	2.01
171	2.26

Example No.	IKK-2 IC_{50} (μM)
172	0.0227
173	3.30
174	7.10
175	8.38
176	>10.0
177	2.12
178	0.0691
179	0.375
180	3.45
181	0.269
182	0.0489
183	0.243
184	0.130
185	0.0258
186	0.139
187	0.0567
188	0.0652
189	0.347
190	0.0734
191	0.0838
192	0.120
193	0.0271
194	2.26
196	1.56
197	3.69
198	0.633
199	0.809
200	0.0256
201	5.77
202	1.50

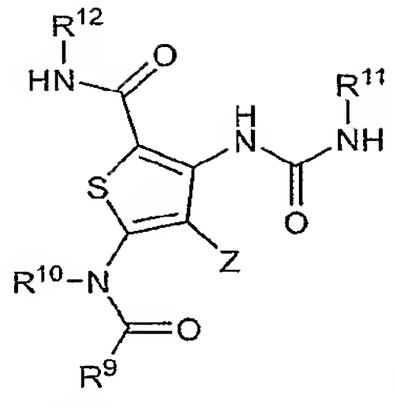
Example No.	IKK-2 IC_{50} (μM)
203	0.103
204	0.120
205	0.0776
206	0.116
207	13.6
208	0.177
209	0.188
210	0.175
211	0.0436
212	0.846
213	0.438
214	0.0715
214.1	0.105
214.2	0.154
214.3	0.105
215	0.392
216	0.286
217	0.198
218	0.709
300	1.24
303	1.18
304	8.72
305	8.13
306	2.09
307	1.70
308	2.51
309	4.10
310	8.16
311	3.33
312	4.82

WHAT IS CLAIMED IS:

1. A compound of Formula IIA or Formula IIB:



IIA



IIB

wherein Z is selected from the group consisting of hydrido, halo, alkyl, cyano, and haloalkyl;

wherein R^9 is selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, or where R^9 and R^{10} together with the atoms to which they are attached form a heterocyclic moiety;

wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-alkylamino, N,N-dialkylamino, N-arylamino, N-alkyl-N-arylamino, N-hydroxyamino, N-alkyl-N-hydroxyamino, N-aryl-N-hydroxyamino, halo, cyano, keto, hydroxyl, alkyl, haloalkyl, cycloalkyl, alkoxy, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, alkoxycarbonyl, aryloxycarbonyl, carboxyl, alkoxyalkoxycarbonyl, alkoxycarbonylamino, heterocycloalkyl, heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloalkylthio, cycloalkylsulfinyl, cycloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heterocycloalkylthio, heterocycloalkylsulfinyl, heterocycloalkylsulfonyl, heteroarylthio, heteroarylsulfinyl, and heteroarylsulfonyl;

wherein R^{10} is selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl, or R^{10} and R^9 together with the atoms to which they are attached form a heterocyclic moiety;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein Z is selected from the group consisting of hydrido, halo, c_{1-6} alkyl, cyano, and c_{1-6} haloalkyl;

wherein R^9 is selected from the group consisting of c_{1-6} alkyl, c_{3-12} cycloalkyl, c_{2-6} alkenyl, c_{3-12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, c_{3-12} aryl, c_{4-18} aralkyl, 3- to 12-membered heteroaryl, and 4- to 18-membered heteroaralkyl, or where R^9 and R^{10} together with the atoms to which they are attached form a 3- to 12-membered heterocyclic moiety;

wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{3-12} aryl)amino, N-(c_{1-6} alkyl)-N-(C_{3-12} aryl)amino, N-hydroxyamino, N-(c_{1-6} alkyl)-N-hydroxyamino, N-(c_{3-12} aryl)-N-hydroxyamino, halo, cyano, keto, hydroxyl, c_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, c_{2-6} alkenyl, c_{2-6} alkenyloxy, c_{3-12} aryl, c_{3-12} aryloxy, c_{4-20} aralkyl, c_{4-20} aralkylcarbonyl, c_{4-20} aralkylcarbonylamino, 3- to 14-membered heteroarylcarbonyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 3- to 12-

membered heteroaryl, C_{2-7} alkoxycarbonyl, C_{3-12} aryloxycarbonyl, carboxyl, C_{2-15} alkoxyalkoxycarbonyl, C_{2-7} alkoxycarbonylamino, 3- to 12-membered heterocycloalkyl, 4- to 18-membered heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{3-12} cycloalkylthio, C_{3-12} cycloalkylsulfinyl, C_{3-12} cycloalkylsulfonyl, C_{3-12} arylthio, C_{3-12} arylsulfinyl, C_{3-12} arylsulfonyl, 3- to 12-membered heterocycloalkylthio, 3- to 12-membered heterocycloalkylsulfinyl, 3- to 12-membered heterocycloalkylsulfonyl, 3- to 12-membered heteroarylthio, 3- to 12-membered heteroarylsulfinyl, and 3- to 12-membered heteroarylsulfonyl;

wherein R^{10} is selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl, or R^{10} and R^9 together with the atoms to which they are attached form a 3- to 12-membered heterocyclic moiety;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-12} aryl, and 3- to 12-membered heteroaryl.

3. A compound according to claim 2 wherein Z is selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyano, and haloalkyl;

wherein R^9 is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, pentenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, phenylethyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl, or where R^9 and R^{10} together with the atoms to which they are attached form pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, or oxazolidinyl;

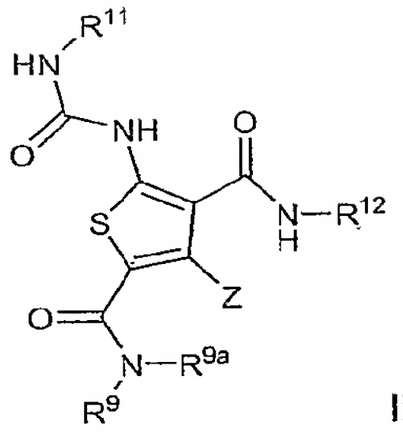
wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-methylamino, N-ethylamino, N-propylamino, N,N-dimethylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N,N-diethylamino, N-ethyl-N-propylamino, N,N-dipropylamino, N-phenylamino, N-biphenylamino, N-naphthylamino, N-methyl-N-phenylamino, N-ethyl-N-phenylamino, N-propyl-N-phenylamino, N-hydroxyamino, N-methyl-N-hydroxyamino, N-ethyl-N-hydroxyamino, N-propyl-N-hydroxyamino, N-phenyl-N-hydroxyamino, N-biphenyl-N-hydroxyamino, N-naphthyl-N-hydroxyamino, chloro, fluoro, bromo, iodo, cyano, keto, hydroxyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, ethenyl, propenyl, butenyl, pentenyl ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, phenyl, biphenyl, naphthyl, indenyl, phenoxy, biphenoxy, naphthyloxy, indenyloxy, benzyl, phenylethyl, benzylcarbonyl, phenylethylcarbonyl, benzylcarbonylamino, phenylethylcarbonylamino, pyridinylcarbonyl, benzothiophenylcarbonyl, indolylcarbonyl,

isoquinolinylcarbonyl, quinolinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl, pyrazolylcarbonyl, imidazolylcarbonyl, isoxazolylcarbonyl, oxazolylcarbonyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, phenoxycarbonyl, biphenoxycarbonyl, naphthyloxycarbonyl, indenyloxycarbonyl, carboxyl, methoxymethoxycarbonyl, methoxyethoxycarbonyl, ethoxymethoxycarbonyl, ethoxyethoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, piperidinylmethyl, piperidinylethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrazolidinylmethyl, pyrazolidinylethyl, imidazolidinylmethyl, imidazolidinylethyl, isoxazolidinylmethyl, isoxazolidinylethyl, oxazolidinylmethyl, oxazolidinylethyl, thiol, oxidosulfanyl, sulfino, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cyclopropylsulfinyl, cyclobutylsulfinyl, cyclopentylsulfinyl, cyclohexylsulfinyl, cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl, phenylthio, biphenylthio, naphthylthio, phenylsulfinyl, biphenylsulfinyl, naphthylsulfinyl, phenylsulfonyl, biphenylsulfonyl, naphthylsulfonyl, piperidinylthio, pyrrolidinylthio, pyrazolidinylthio, imidazolidinylthio, isoxazolidinylthio, oxazolidinylthio, piperidinylsulfinyl, pyrrolidinylsulfinyl, pyrazolidinylsulfinyl, imidazolidinylsulfinyl, isoxazolidinylsulfinyl, oxazolidinylsulfinyl, piperidinylsulfonyl, pyrrolidinylsulfonyl, pyrazolidinylsulfonyl, imidazolidinylsulfonyl, isoxazolidinylsulfonyl, oxazolidinylsulfonyl, pyridinylthio, benzothiophenylthio, indolylthio, isoquinolinylthio, quinolinylthio, thienylthio, pyrrolylthio, furylthio, pyrazolylthio, imidazolylthio, isoxazolylthio, oxazolylthio, isoindoledionylthio, pyridinylsulfinyl, benzothiophenylsulfinyl, indolylsulfinyl, isoquinolinylsulfinyl, quinolinylsulfinyl, thienylsulfinyl, pyrrolylsulfinyl, furylsulfinyl, pyrazolylsulfinyl, imidazolylsulfinyl, isoxazolylsulfinyl, oxazolylsulfinyl, isoindoledionylsulfinyl, pyridinylsulfonyl, benzothiophenylsulfonyl, indolylsulfonyl, isoquinolinylsulfonyl, quinolinylsulfonyl, thienylsulfonyl, pyrrolylsulfonyl, furylsulfonyl, pyrazolylsulfonyl, imidazolylsulfonyl, isoxazolylsulfonyl, oxazolylsulfonyl, and isoindoledionylsulfonyl;

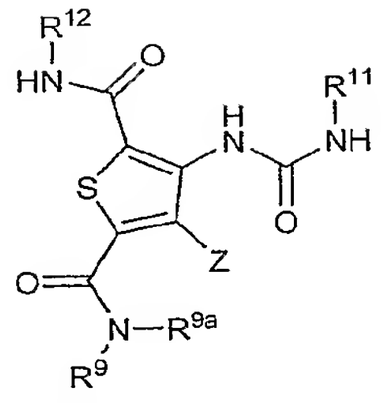
wherein R^{10} is selected from the group consisting of hydrido; hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, or R^{10} and R^{9} together with the atoms to which they are attached form a cyclic moiety selected from the group consisting of piperidinonyl, dihydropyridinonyl, pyridinonyl, dihydroindolonyl, octahydroindolonyl, dihydroisoindolonyl, octahydroisoindolonyl, isoquinolinonyl, dihydroisoquinolinonyl, quinolinonyl, dihydroquinolinonyl, pyrrolidinonyl, and pyrazolidinonyl;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl.

4. A compound of Formula IIC or Formula IID:



IIC



IID

wherein Z is selected from the group consisting of hydrido, halo, alkyl, cyano, and haloalkyl;

wherein R^9 is selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, or where R^9 and R^{9a} together with the nitrogen to which they are attached form a heterocyclic moiety;

wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-alkylamino, N,N-dialkylamino, N-arylamino, N-alkyl-N-arylamino, N-hydroxyamino, N-alkyl-N-hydroxyamino, N-aryl-N-hydroxyamino, halo, cyano, keto, hydroxyl, alkyl, haloalkyl, cycloalkyl, alkoxy, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, alkoxycarbonyl, aryloxycarbonyl, carboxyl, alkoxyalkoxycarbonyl, alkoxycarbonylamino, heterocycloalkyl, heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloalkylthio, cycloalkylsulfinyl, cycloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heterocycloalkylthio, heterocycloalkylsulfinyl, heterocycloalkylsulfonyl, heteroarylthio, heteroarylsulfinyl, and heteroarylsulfonyl;

wherein R^{9a} is selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl, or where R^{9a} and R^9 together with the nitrogen to which they are attached form a heterocyclic moiety;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 wherein Z is selected from the group consisting of hydrido, halo, c_{1-6} alkyl, cyano, and c_{1-6} haloalkyl;

wherein R^9 is selected from the group consisting of c_{1-6} alkyl, c_{3-12} cycloalkyl, c_{2-6} alkenyl, c_{3-12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, c_{3-12} aryl, c_{4-18} aralkyl, 3- to 12-membered heteroaryl, and 4- to 18-membered heteroaralkyl, or where R^9 and R^{9a} together with the nitrogen to which they are attached form a 3- to 12-membered heterocyclic moiety;

wherein R^9 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{3-12} aryl)amino, N-(c_{1-6} alkyl)-N-(C_{3-12} aryl)amino, N-hydroxyamino, N-(c_{1-6} alkyl)-N-hydroxyamino, N-(c_{3-12} aryl)-N-hydroxyamino, halo, cyano, keto, hydroxyl, c_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, c_{2-6} alkenyl, c_{2-6} alkenyloxy, c_{3-12} aryl, c_{3-12} aryloxy, c_{4-20} aralkyl, c_{4-20} aralkylcarbonyl, c_{4-20} aralkylcarbonylamino, 3- to 14-membered heteroarylcarbonyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 3- to 12-membered heteroaryl, c_{2-7} alkoxycarbonyl, c_{3-12} aryloxycarbonyl, carboxyl, c_{2-15} alkoxyalkoxycarbonyl, c_{2-7} alkoxycarbonylamino, 3- to 12-membered heterocycloalkyl, 4- to 18-membered heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, c_{3-12} cycloalkylthio, c_{3-12} cycloalkylsulfinyl, c_{3-12} cycloalkylsulfonyl, c_{3-12} arylthio, c_{3-12} arylsulfinyl, c_{3-12} arylsulfonyl, 3- to 12-

membered heterocycloalkylthio, 3- to 12-membered heterocycloalkylsulfinyl, 3- to 12-membered heterocycloalkylsulfonyl, 3- to 12-membered heteroarylthio, 3- to 12-membered heteroarylsulfinyl, and 3- to 12-membered heteroarylsulfonyl;

wherein R^{9a} is selected from the group consisting of hydrido, hydroxyl, c_{1-6} alkoxy, c_{1-6} alkyl, c_{1-6} haloalkyl, c_{3-12} aryl, and 3- to 12-membered heteroaryl, or where R^{9a} and R^{9} together with the nitrogen to which they are attached form a 3- to 12-membered heterocyclic moiety;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, c_{1-6} alkoxy, c_{1-6} alkyl, c_{1-6} haloalkyl, c_{3-12} aryl, and 3- to 12-membered heteroaryl.

6. A compound according to claim 5 wherein Z is selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyano, and haloalkyl;

wherein R^{9} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, pentenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, phenylethyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl, or where R^{9} and R^{9a} together with the atoms to which they are attached form a cyclic moiety selected from the group consisting of piperidinonyl, dihydropyridinonyl, pyridinonyl, dihydroindolonyl, octahydroindolonyl, dihydroisoindolonyl, octahydroisoindolonyl, isoquinolinonyl, dihydroisoquinolinonyl, quinolinonyl, dihydroquinolinonyl, pyrrolidinonyl, and pyrazolidinonyl;

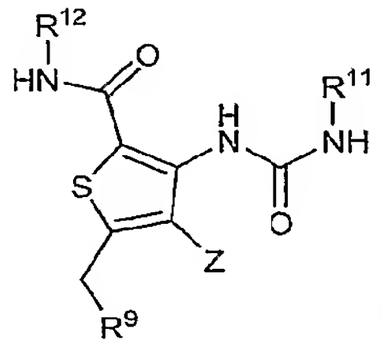
wherein R^{9} is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-methylamino, N-ethylamino, N-propylamino, N,N-dimethylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N,N-diethylamino, N-ethyl-N-propylamino, N,N-dipropylamino, N-phenylamino, N-biphenylamino, N-naphthylamino, N-methyl-N-phenylamino, N-ethyl-N-phenylamino, N-propyl-N-phenylamino, N-hydroxyamino, N-methyl-N-hydroxyamino, N-ethyl-N-hydroxyamino, N-propyl-N-hydroxyamino, N-phenyl-N-hydroxyamino, N-biphenyl-N-hydroxyamino, N-naphthyl-N-hydroxyamino, chloro, fluoro, bromo, iodo, cyano, keto, hydroxyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, ethenyl, propenyl, butenyl, pentenyl ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, phenyl, biphenyl, naphthyl, indenyl, phenoxy, biphenoxy, naphthyloxy, indenyloxy, benzyl, phenylethyl, benzylcarbonyl, phenylethylcarbonyl, benzylcarbonylamino, phenylethylcarbonylamino, pyridinylcarbonyl, benzothiophenylcarbonyl, indolylcarbonyl, isoquinolinylcarbonyl, quinolinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl, pyrazolylcarbonyl, imidazolylcarbonyl, isoxazolylcarbonyl, oxazolylcarbonyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl,

isoxazolidinyl, oxazolidinyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, phenoxycarbonyl, biphenoxycarbonyl, naphthyloxycarbonyl, indenyloxycarbonyl, carboxyl, methoxymethoxycarbonyl, methoxyethoxycarbonyl, ethoxymethoxycarbonyl, ethoxyethoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, piperidinylmethyl, piperidinylethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrazolidinylmethyl, pyrazolidinylethyl, imidazolidinylmethyl, imidazolidinylethyl, isoxazolidinylmethyl, isoxazolidinylethyl, oxazolidinylmethyl, oxazolidinylethyl, thiol, oxidosulfanyl, sulfino, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cyclopropylsulfinyl, cyclobutylsulfinyl, cyclopentylsulfinyl, cyclohexylsulfinyl, cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl, phenylthio, biphenylthio, naphthylthio, phenylsulfinyl, biphenylsulfinyl, naphthylsulfinyl, phenylsulfonyl, biphenylsulfonyl, naphthylsulfonyl, piperidinylthio, pyrrolidinylthio, pyrazolidinylthio, imidazolidinylthio, isoxazolidinylthio, oxazolidinylthio, piperidinylsulfinyl, pyrrolidinylsulfinyl, pyrazolidinylsulfinyl, imidazolidinylsulfinyl, isoxazolidinylsulfinyl, oxazolidinylsulfinyl, piperidinylsulfonyl, pyrrolidinylsulfonyl, pyrazolidinylsulfonyl, imidazolidinylsulfonyl, isoxazolidinylsulfonyl, oxazolidinylsulfonyl, pyridinylthio, benzothiophenylthio, indolylthio, isoquinolinylthio, quinolinylthio, thienylthio, pyrrolylthio, furylthio, pyrazolylthio, imidazolylthio, isoxazolylthio, oxazolylthio; isoindoledionylthio, pyridinylsulfinyl, benzothiophenylsulfinyl, indolylsulfinyl, isoquinolinylsulfinyl, quinolinylsulfinyl, thienylsulfinyl, pyrrolylsulfinyl, furylsulfinyl, pyrazolylsulfinyl, imidazolylsulfinyl, isoxazolylsulfinyl, oxazolylsulfinyl, isoindoledionylsulfinyl, pyridinylsulfonyl, benzothiophenylsulfonyl, indolylsulfonyl, isoquinolinylsulfonyl, quinolinylsulfonyl, thienylsulfonyl, pyrrolylsulfonyl, furylsulfonyl, pyrazolylsulfonyl, imidazolylsulfonyl, isoxazolylsulfonyl, oxazolylsulfonyl, and isoindoledionylsulfonyl;

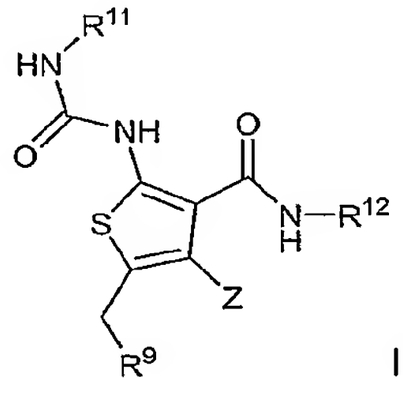
wherein R^{9a} is selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl, or where R^{9a} and R^{9} together with the nitrogen to which they are attached form pyridine, piperidine, indole, indoline, isoindole, isoindolinyl, isoquinoline, quinoline, pyrrole, pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, isoxazole, isoxazolidine, oxazole, or oxazolidine;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl.

7. A compound of Formula IIE or IIF:



IIE



IIF

wherein Z is selected from the group consisting of hydrido, halo, alkyl, cyano, and haloalkyl;

wherein R^1 is selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-alkylamino, N,N-dialkylamino, N-arylamino, N-alkyl-N-arylamino, N-hydroxyamino, N-alkyl-N-hydroxyamino, N-aryl-N-hydroxyamino, halo, cyano, keto, hydroxyl, alkyl, haloalkyl, cycloalkyl, alkoxy, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, alkoxycarbonyl, aryloxycarbonyl, carboxyl, alkoxyalkoxycarbonyl, alkoxycarbonylamino, heterocycloalkyl, heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloalkylthio, cycloalkylsulfinyl, cycloalkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heterocycloalkylthio, heterocycloalkylsulfinyl, heterocycloalkylsulfonyl, heteroarylthio, heteroarylsulfinyl, and heteroarylsulfonyl;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 7 wherein Z is selected from the group consisting of hydrido, halo, c_{1-6} alkyl, cyano, and c_{1-6} haloalkyl;

wherein R^1 is selected from the group consisting of c_{1-6} alkyl, c_{3-12} cycloalkyl, c_{2-6} alkenyl, c_{3-12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, c_{3-12} aryl, c_{4-18} aralkyl, 3- to 12-membered heteroaryl, and 4- to 18-membered heteroaralkyl;

wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(C_{3-12} aryl)amino, N-(c_{1-6} alkyl)-N-(C_{3-12} aryl)amino, N-hydroxyamino, N-(c_{1-6} alkyl)-N-hydroxyamino, N-(c_{3-12} aryl)-N-hydroxyamino, halo, cyano, keto, hydroxyl, c_{1-6} alkyl, c_{1-6} haloalkyl, C_{3-6} cycloalkyl, c_{1-6} alkoxy, c_{2-6} alkenyl, c_{2-6} alkenyloxy, c_{3-12} aryl, c_{3-12} aryloxy, c_{4-20} aralkyl, c_{4-20} aralkylcarbonyl, c_{4-20} aralkylcarbonylamino, 3- to 14-membered heteroarylcarbonyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 3- to 12-membered heteroaryl, c_{2-7} alkoxycarbonyl, c_{3-12} aryloxycarbonyl, carboxyl, c_{2-15} alkoxyalkoxycarbonyl, c_{2-7} alkoxycarbonylamino, 3- to 12-membered heterocycloalkyl, 4- to 18-membered heterocycloalkylalkyl, thiol, oxidosulfanyl, sulfino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, c_{3-12} cycloalkylthio, c_{3-12} cycloalkylsulfinyl, c_{3-12} cycloalkylsulfonyl, c_{3-12} arylthio, c_{3-12} arylsulfinyl, c_{3-12} arylsulfonyl, 3- to 12-membered heterocycloalkylthio, 3- to 12-membered heterocycloalkylsulfinyl, 3- to 12-membered heterocycloalkylsulfonyl, 3- to 12-membered heteroarylthio, 3- to 12-membered heteroarylsulfinyl, and 3- to 12-membered heteroarylsulfonyl;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, c_{1-6} alkoxy, c_{1-6} alkyl, c_{1-6} haloalkyl, c_{3-12} aryl, and 3- to 12-membered heteroaryl.

9. A compound according to claim 8 wherein Z is selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyano, and haloalkyl;

wherein R^1 is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, pentenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl,

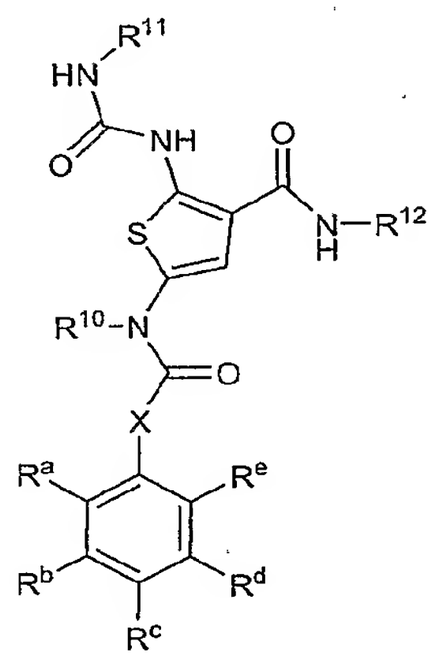
dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, phenylethyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl;

wherein R^1 is optionally substituted by one or more substituents independently selected from the group consisting of amino, N-methylamino, N-ethylamino, N-propylamino, N,N-dimethylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N,N-diethylamino, N-ethyl-N-propylamino, N,N-dipropylamino, N-phenylamino, N-biphenylamino, N-naphthylamino, N-methyl-N-phenylamino, N-ethyl-N-phenylamino, N-propyl-N-phenylamino, N-hydroxyamino, N-methyl-N-hydroxyamino, N-ethyl-N-hydroxyamino, N-propyl-N-hydroxyamino, N-phenyl-N-hydroxyamino, N-biphenyl-N-hydroxyamino, N-naphthyl-N-hydroxyamino, chloro, fluoro, bromo, iodo, cyano, keto, hydroxyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, ethenyl, propenyl, butenyl, pentenyl ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, phenyl, biphenyl, naphthyl, indenyl, phenoxy, biphenoxy, naphthyloxy, indenyloxy, benzyl, phenylethyl, benzylcarbonyl, phenylethylcarbonyl, benzylcarbonylamino, phenylethylcarbonylamino, pyridinylcarbonyl, benzothiophenylcarbonyl, indolylcarbonyl, isoquinolinylcarbonyl, quinolinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl, pyrazolylcarbonyl, imidazolylcarbonyl, isoxazolylcarbonyl, oxazolylcarbonyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindolinyl, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, phenoxycarbonyl, biphenoxycarbonyl, naphthyloxycarbonyl, indenyloxycarbonyl, carboxyl, methoxymethoxycarbonyl, methoxyethoxycarbonyl, ethoxymethoxycarbonyl, ethoxyethoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, piperidinylmethyl, piperidinylethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrazolidinylmethyl, pyrazolidinylethyl, imidazolidinylmethyl, imidazolidinylethyl, isoxazolidinylmethyl, isoxazolidinylethyl, oxazolidinylmethyl, oxazolidinylethyl, thiol, oxidosulfanyl, sulfino, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cyclopropylsulfinyl, cyclobutylsulfinyl, cyclopentylsulfinyl, cyclohexylsulfinyl, cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl, phenylthio, biphenylthio, naphthylthio, phenylsulfinyl, biphenylsulfinyl, naphthylsulfinyl, phenylsulfonyl, biphenylsulfonyl, naphthylsulfonyl, piperidinylthio, pyrrolidinylthio, pyrazolidinylthio, imidazolidinylthio, isoxazolidinylthio, oxazolidinylthio, piperidinylsulfinyl, pyrrolidinylsulfinyl, pyrazolidinylsulfinyl, imidazolidinylsulfinyl, isoxazolidinylsulfinyl, oxazolidinylsulfinyl, piperidinylsulfonyl, pyrrolidinylsulfonyl, pyrazolidinylsulfonyl, imidazolidinylsulfonyl, isoxazolidinylsulfonyl, oxazolidinylsulfonyl, pyridinylthio, benzothiophenylthio, indolylthio, isoquinolinylthio, quinolinylthio, thienylthio, pyrrolylthio, furylthio, pyrazolylthio, imidazolylthio, isoxazolylthio, oxazolylthio, isoindoledionylthio, pyridinylsulfinyl, benzothiophenylsulfinyl, indolylsulfinyl, isoquinolinylsulfinyl, quinolinylsulfinyl, thienylsulfinyl, pyrrolylsulfinyl, furylsulfinyl, pyrazolylsulfinyl, imidazolylsulfinyl, isoxazolylsulfinyl, oxazolylsulfinyl, isoindoledionylsulfinyl,

pyridinylsulfonyl, benzothiophenylsulfonyl, indolylsulfonyl, isoquinolinylsulfonyl, quinolinylsulfonyl, thienylsulfonyl, pyrrolylsulfonyl, furylsulfonyl, pyrazolylsulfonyl, imidazolylsulfonyl, isoxazolylsulfonyl, oxazolylsulfonyl, and isoindoledionylsulfonyl;

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl.

10. A compound of Formula III:



III

wherein X is a bond or alkyl;

wherein R^a is selected from the group consisting of halo, cyano, alkyl, cycloalkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkoxy, alkoxycarbonyl, carboxyl, heterocycloalkylalkyl, and alkylsulfonyl, or wherein R^a and R^{10} together with the atoms to which they are attached form a heterocyclic moiety;

wherein R^b, R^c, R^d, and R^e are independently selected from the group consisting of halo, cyano, alkyl, cycloalkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkoxy, alkoxycarbonyl, carboxyl, heterocycloalkylalkyl, and alkylsulfonyl;

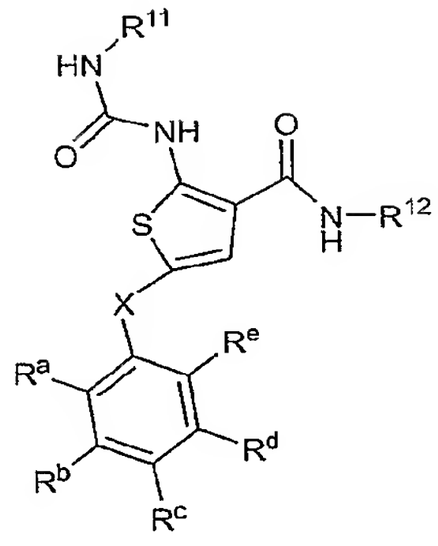
wherein R^{10} is selected from the group consisting of hydrido and alkyl, or R^{10} and R^a together with the atoms to which they are attached form a heterocyclic moiety; and

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and alkyl;

wherein R^a and R^b, or R^b and R^c, or R^c and R^d, or R^d and R^e may form a ring moiety fused to the phenyl ring to which they are both attached, said ring moiety selected from the group consisting of cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein said ring moiety may be substituted by one or more substituents selected from the group consisting of halo, keto, alkyl, hydroxy, alkoxy, aralkyl, and aralkoxy;

or a pharmaceutically acceptable salt thereof.

11. A compound of Formula IV:



IV

wherein X is alkyl;

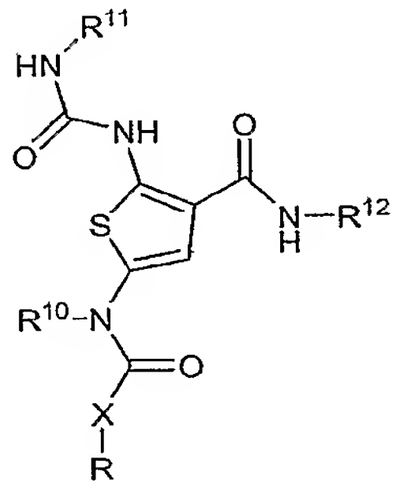
wherein R^a, R^b, R^c, R^d, and R^e are independently selected from the group consisting of halo, cyano, alkyl, haloalkyl, alkoxy, aryl, and aralkoxy; and

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and alkyl;

wherein R^a and R^b, or R^b and R^c, or R^c and R^d, or R^d and R^e may form an aryl moiety fused to the phenyl ring to which they are both attached, wherein said aryl moiety may be substituted by one or more substituents selected from the group consisting of halo, alkyl, and alkoxy;

or a pharmaceutically acceptable salt thereof.

12. A compound of Formula V:



V

wherein X is a bond or alkyl;

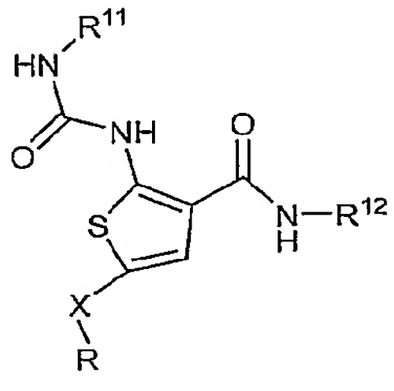
wherein R is a 5- to 12-membered heterocyclic moiety;

wherein R is optionally substituted by one or more substituents independently selected from the group consisting of halo, alkyl, alkoxycarbonyl, carboxyl, and heteroarylalkyl;

wherein R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrido and alkyl;

or a pharmaceutically acceptable salt thereof.

13. A compound of Formula VI:



VII

wherein X is alkyl;

wherein R is selected from the group consisting of alkyl, alkenyl, C_{3-12} cycloalkyl, and C_{3-12} cycloalkenyl;

wherein R is optionally substituted by one or more substituents independently selected from the group consisting of cyano, keto, alkyl, alkoxy, haloalkyl, alkylcarbonyl, aryl, cycloalkyl, aralkylcarbonyl, aralkylcarbonylamino, heteroarylcarbonyl, alkoxycarbonyl, carboxyl, and alkoxyalkoxycarbonyl; and

wherein R^{11} and R^{12} are independently selected from the group consisting of hydrido and alkyl;

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound according to any one of claims 1-13 or a pharmaceutically-acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or adjuvant.

15. A method of treating cancer, inflammation, or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to such cancer, inflammation, or an inflammation-associated disorder, a therapeutically-effective amount of a compound according to any one of claims 1-13.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/001123

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D333/38 C07D409/12 A61K31/381 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/104218 A (SMITHKLINE BEECHAM CORPORATION; CALLAHAN, JAMES, F; LI, YUE, H) 18 December 2003 (2003-12-18)	1-11,14, 15
A	page 5, line 19 - page 8, line 19; examples 5,6	12,13
A	WO 01/58890 A (ASTRAZENECA AB; BAXTER, ANDREW; BROUGH, STEPHEN; FAULL, ALAN; JOHNSTON) 16 August 2001 (2001-08-16) page 4, line 5 - page 6, line 10	1-15
A	WO 03/010158 A (ASTRAZENECA AB; FAULL, ALAN; JOHNSTONE, CRAIG; MORLEY, ANDREW; POYSER,) 6 February 2003 (2003-02-06) page 4, line 19 - page 11, line 10	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 2005	22/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Usuelli, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/001123

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 2004/063186 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; FAULL, ALAN, WELLINGTON; JOHNS) 29 July 2004 (2004-07-29) page 4, line 9 - page 7, line 22	1-15
P,A	WO 2004/063185 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; MORLEY, ANDREW, DAVID; POYSER,) 29 July 2004 (2004-07-29) page 4, line 9 - page 7, line 11	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/001123

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

formation on patent family members

Inter[redacted]onal Application No
PCT/IB2005/001123

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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